VOLUME 44 NUMBER 3

ARCHIVES OF

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SPECIAL NOTICE

Beginning with the October 1950 issue, it is planned to introduce several changes in the covers of all the A. M. A. specialty journals.

The cover of this journal will be white enamel stock with title identification as the A. M. A. Archives of Ophthalmology in color, with date, volume and number also in color. The Table of Contents, which is now carried on the back cover, will be placed in the front of the journal directly preceding the lead article or editorial. Second, third and fourth covers will be used for color advertising.

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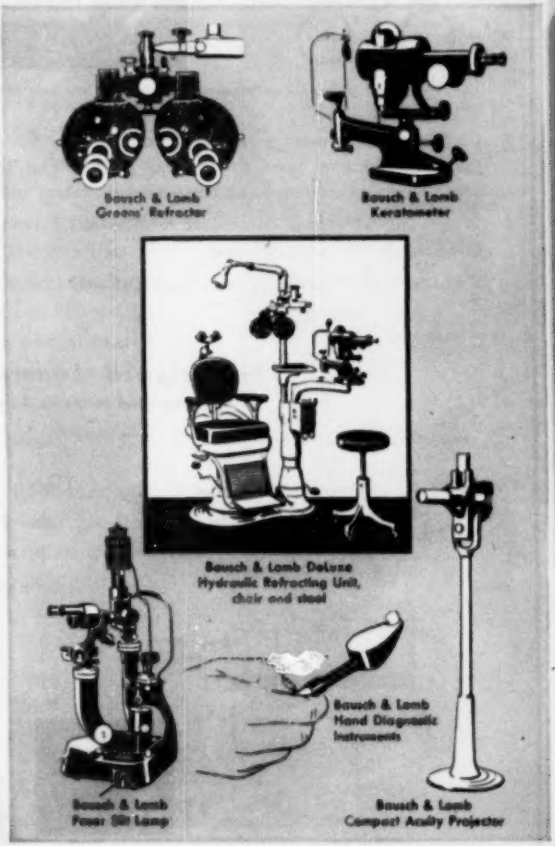
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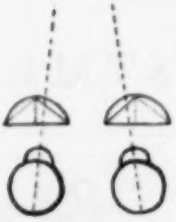

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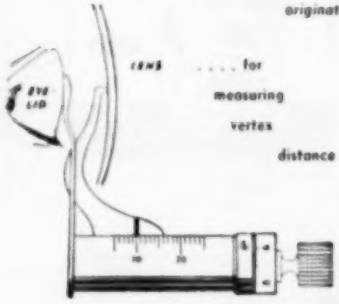

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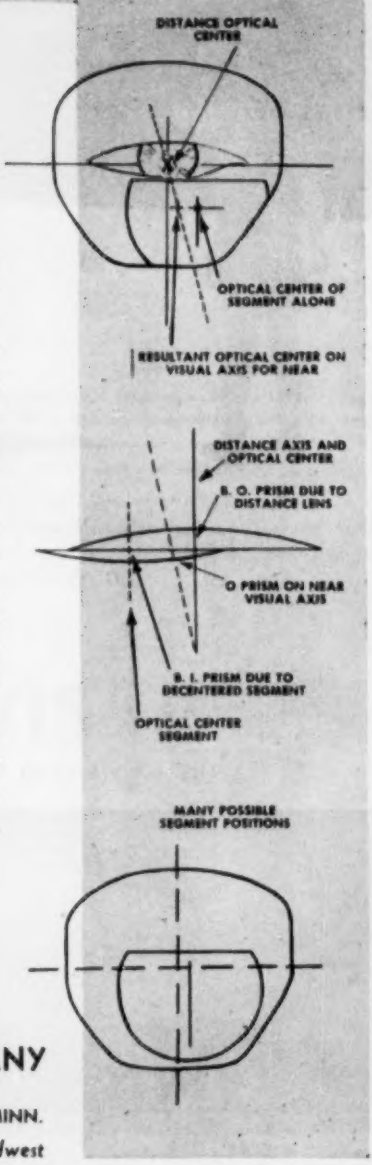
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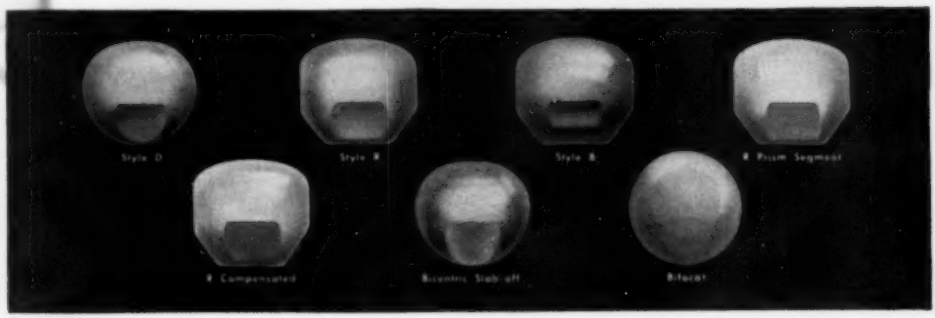

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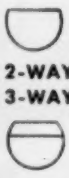

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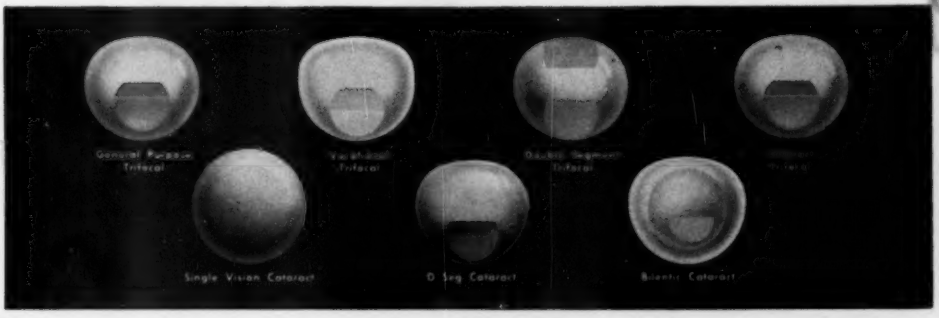

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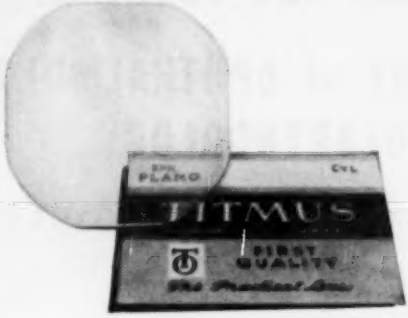

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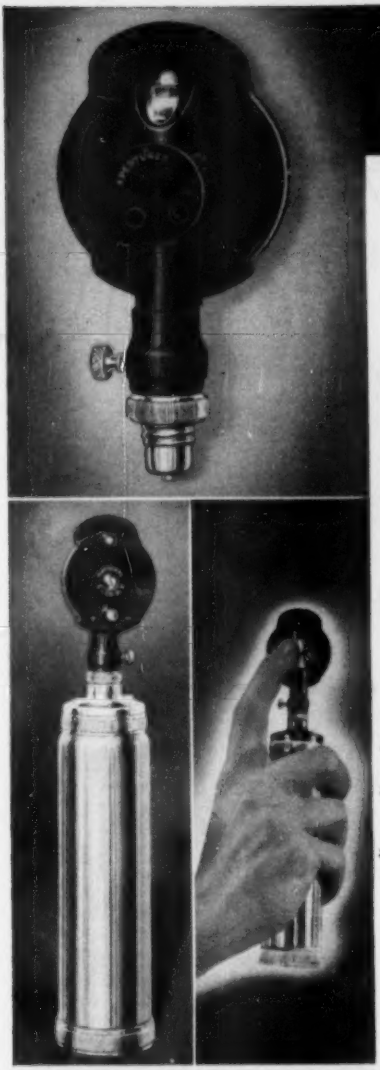

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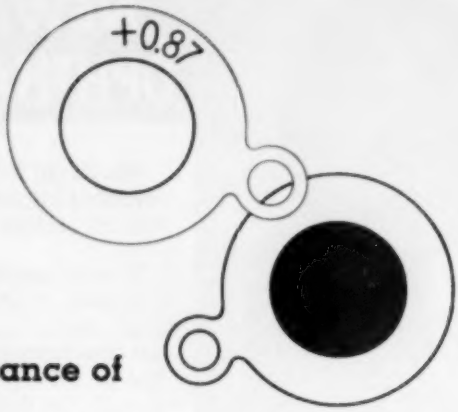

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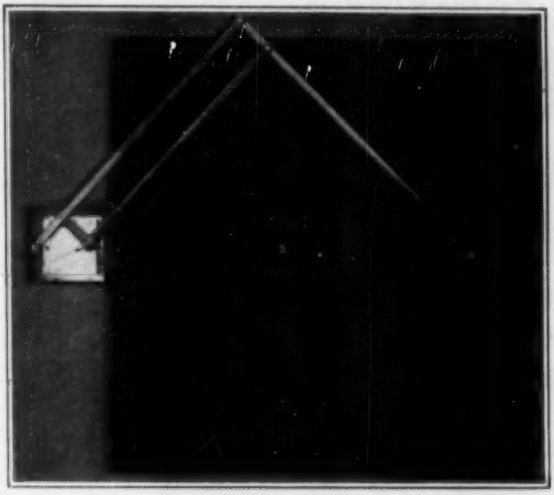

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Since no marks are needed other than the fixation object, the screen may be hung flush against the wall. The blind spots are indicated on the record cards. The pantograph arms are of duralumin with metal bearings so that the latter act freely but are precise.

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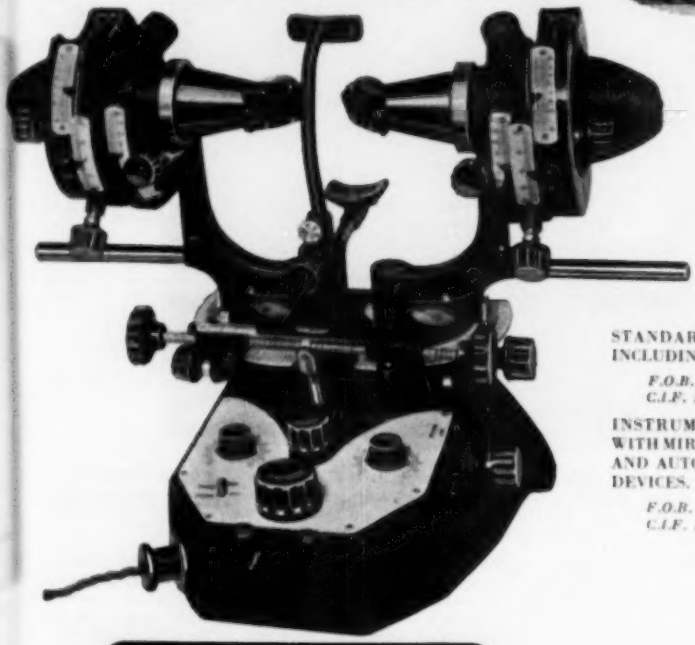

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ARCHIVES OF OPHTHALMOLOGY

VOLUME 44 SEPTEMBER 1950 NUMBER 3

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COMPARISON OF REFRACTION OF STRABISMIC EYES WITH THAT OF NONSTRABISMIC EYES FROM BIRTH TO THE TWENTY-FIFTH YEAR

E. V. L. BROWN, M.D.
CHICAGO

IT HAS long been known that strabismic eyes are predominantly hyperopic in type and tend to remain so. However, there are many exceptions to this rule, and no very detailed study of a goodly number of cases is to be found in the literature. The present paper is an attempt to supply some of these data.

FINDINGS AND COMMENT

The material comprises a year by year study of the average net refraction (hyperopia balanced against myopia) for roughly 1,000 strabismic eyes.[1] These values are compared with values for a control

This paper was presented at the Sixteenth International Ophthalmological Congress, London, July 19, 1950.

Dr. A. C. Krause, professor of ophthalmology and director of the Division of Ophthalmology of the University of Chicago, permitted me to use the clinical data accumulated there, for the most part, prior to World War II, when I was in charge of the work (1926-1941).

1. Each eye was repeatedly studied under atropine cycloplegia (four times a day for four days), and the refraction was compared with that of nonstrabismic eyes. Over the years the number of refractions with atropine cycloplegia averaged over three per person.

On the basis of these actual retinoscopic and trial case findings, computations of the refraction for intervening years (those in which no atropinization was used) were as follows: With, say, + 3.00 D. found at 6 years and + 4.00 D. found at 8 years, an entry of a refraction of + 3.50 D. was made for the age of 7. When astigmatism was present, the refraction of the meridian of greatest curvature was added to that of the least, the sum divided by 2 and the mean recorded as the refraction of the eye for this period. Thus, with the vertical axis showing + 2.00 D. and the horizontal axis + 4.00 D., the mean, + 3.00 D., was recorded as the refraction of the eye.

To arrive at the average yearly net refraction, the total hyperopia and the total myopia were balanced, and this net amount was divided by the number of computations (retinoscopy-trial case findings plus the computations for the year). Altogether, 4,253 such actual determinations and computations of the refraction were made for 521 persons with strabismus and 8,339 such determinations for 738 persons without strabismus. One thousand and fifty-six eyes were studied in the clinic of the University of Chicago and 203 eyes in my private office; 625 patients were males and 634 females. In round numbers, some 2,500 eyes of 1,259 patients had roughly 12,500 refraction estimates made over the years (1 to 24), an average of five refractions a year.

group of some 1,500 eyes without strabismus. This control group, of course, in no sense represents what would be found in an average "normal" eye, for such eyes are seen by the ophthalmologist for the very reason that some one thinks they are not "normal."

Our data [2] (see table and chart) show that, in patients who come to the eye physician the average nonstrabismic eye is hyperopic at birth and continues to be so in each of the first seven years of life. This hyperopia through the first six years of life, including that found at the

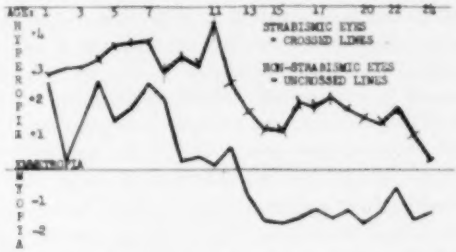
Year by Year Comparison of Average Net Refraction (Hyperopia Plus Myopia), for Ages 1 Through 24

Strabismic Eyes				Nonstrabismic Eyes			
Year	Number of Computations	Refraction, in Diopters	Type	Year	Number of Computations	Refraction, in Diopters	Type
1	91	2.80	Hyperopia	1	6	5.50	Hyperopia
2	123	3.07	Hyperopia	2	17	0.17	Hyperopia
3	173	3.12	Hyperopia	3	10	1.34	Hyperopia
4	139	3.35	Hyperopia	4	60	2.71	Hyperopia
5	140	3.79	Hyperopia	5	80	1.45	Hyperopia
6	111	2.86	Hyperopia	6	84	1.97	Hyperopia
7	405	3.92	Hyperopia	7	446	2.64	Hyperopia
8	372	2.99	Hyperopia	8	527	2.14	Hyperopia
9	397	3.45	Hyperopia	9	495	0.21	Hyperopia
10	397	3.18	Hyperopia	10	508	0.28	Hyperopia
11	258	4.49	Hyperopia	11	585	0.05	Hyperopia
12	278	2.04	Hyperopia	12	616	0.05	Hyperopia
13	289	1.78	Hyperopia	13	544	0.98	Myopia
14	279	1.19	Hyperopia	14	434	1.61	Myopia
15	269	1.12	Hyperopia	15	403	1.68	Myopia
16	147	1.97	Hyperopia	16	430	1.51	Myopia
17	125	1.90	Hyperopia	17	478	1.27	Myopia
18	96	2.15	Hyperopia	18	345	1.48	Myopia
19	79	1.87	Hyperopia	19	377	1.32	Myopia
20	57	1.54	Hyperopia	20	354	1.60	Myopia
21	38	1.33	Hyperopia	21	334	1.31	Myopia
22	16	1.80	Hyperopia	22	276	0.57	Myopia
23	12	1.02	Hyperopia	23	208	1.47	Myopia
24	19	0.36	Myopia	24	263	1.29	Myopia

2. Over the years my associates and I have made extended studies of refraction of atropinized eyes. The adult material has been much increased by the use of atropine first in one eye and then, a month later, in the other, in keeping with a procedure which I devised in 1913. The present article is a restudy of much of the same material as that used in the previous publications. Brown, E. V. L., and Kronfeld, P. C.: The Refraction Curve in the United States, with Special Reference to Changes in the First Two Decades, Compte-rendu du XIII Concilium Ophthalmologicum Amsterdam-den Haag, 1929, vol. 1, p. 87. Kronfeld, P. C., and Devney, C.: Ein Beitrag zur Kenntnis der Refractionskurve, Arch. f. Ophth. **126**:487-501, 1931; The Frequency of Astigmatism, Arch. Ophth. **4**:873-884 (Dec.) 1930. Bothman, L.: Refraction Changes in the Eyes of Children Under Six Years of Age, ibid. **7**:294-296 (Feb.) 1932; Homatropine and Atropine Cycloplegia, ibid. **7**:389-398 (March) 1932. Brown, E. V. L.: Apparent Increase of Hyperopia up to the Age of Nine Years, Am. J. Ophth. **19**:1106 (1936); Net Average Yearly Changes in Refraction of Atropinized Eyes from Birth to Beyond Middle Life, Arch. Ophth. **19**:719-734 (May) 1938; Use-Abuse Theory of Changes in Refraction Versus Biologic Theory, Arch. Ophth. **28**:845-850 (Nov.) 1942.

first and subsequent examinations and the computations made for intervening years, averages +1.89 D. and contrasts strongly with the +3.36 D. found in strabismic eyes. Our strabismic eyes, therefore, have about 80 per cent more hyperopia than have nonstrabismic eyes in the first six years of life. However, the number of observations and computations on the nonstrabismic eyes is very small, and the yearly variation in refraction is large, so that these data must be looked on as inconclusive. Still, the seventh year, with seemingly adequate data, shows the same sharp contrast, e. g., +3.92 D. for the strabismic and +2.64 D. for the nonstrabismic eyes; i. e., during the seventh year there is 48 per cent more hyperopia in the strabismic eyes, and more data may prove that the figures for 1 to 6 years are also essentially correct.

During the next four years of life, 8 through 11, this contrast continues and becomes even more marked; indeed, it sets the refraction of the strabismic eye apart as definitely anomalous. Our data show a



Comparison of the refraction of strabismic eyes with that of nonstrabismic eyes from birth to the twenty-fifth year.

high, relatively static hyperopia for the strabismic eye, averaging +3.46 D., with the refraction of the nonstrabismic eye now moving rapidly toward the myopic side and averaging only +0.64 D., a difference of nearly 3 D. This decrease of hyperopia in the nonstrabismic eye is greatest during the ninth year, with +2.14 D. found at the end of the eighth and +0.21 D. found at the end of the ninth year, a drop of + 1.93 D., or over nine tenths of its hyperopia in one year! In contrast, the average strabismic eye loses only a ¼ to ½ D., or one tenth of its hyperopia, from 8 through 11 years. The condition of the strabismic eye stands still, or barely moves toward emmetropia, at this time. In view of these findings, a study of the process in relation to puberty and its expression in the respective sexes might be in order.

From 12 through 15 the strabismic eye also shows a regular decrease of its hyperopia. It moves from +4.49 down to +1.12 D. and so loses 75 per cent of its hyperopia. It thus also conforms to the "rule

of emmetropization."[3] In the twelfth year the largest amount is lost, from +4.49 to +2.64 D., but this is only 41 per cent. Overall, (1) the process (loss of hyperopia) is deferred four years, from the eighth to the twelfth, in strabismic eyes, as compared with nonstrabismic eyes, and (2) the loss is less precipitous in the year of greatest expression—only 41 per cent for the twelfth year, as compared with 90 per cent for the ninth year in nonstrabismic eyes. Meanwhile, the nonstrabismic eye has become more myopic and moves from —0.65 to —1.68 D.

Beyond the fifteenth year the number of our strabismus computations decreases rapidly though it is still considerable and probably reliable through 16 and 17 years. Observations on nonstrabismic eyes are numerous enough and show variations of only ¼ D. of increase or decrease from year to year. But no increase of myopia beyond that found in the twentieth year (—1.60 D.) takes place.

For the period as a whole, up to the end of the twenty-fourth year the net average refraction of our strabismic eyes is +2.69 D., and that of our nonstrabismic eyes, —0.47 D., a difference of 3.16 D. As stated, the number of observations and computations for nonstrabismic eyes before the age of 7 and that for strabismic eyes after the age of 17 is rather too small to warrant fully reliable conclusions; but between the ages of 7 and 17, inclusive, the material is ample. Here net average refraction of the strabismic eyes is +2.71 D., and that of the nonstrabismic eyes, —0.20 D.—a net difference of +2.91 D.

Why hyperopia and strabismus are so closely associated and what the significance is of this association are questions beyond the scope and intent of this paper.

CONCLUSIONS

The refraction of strabismic eyes is compared with that of nonstrabismic eyes under atropine cycloplegia and the net hyperopia or myopia is presented in a table and graph for each age year up to 25. The material consists of over 1,000 strabismic eyes and 1,500 nonstrabismic eyes. I reach the following conclusions:

1. The amount of hyperopia present in the strabismic eye in excess of that in the nonstrabismic eye is surprisingly large, averaging over +3.00 D. up to the age of 25.

2. The strabismic eye loses much of its early hyperopia, "undergoes emmetropization" and even moves a bit over onto the myopic side if anything, before the age of 25.

3. The timing of the change differs from that found in the nonstrabismic eye. It comes only after the eleventh year in the strabismic

3. Falkenburg, J., and Straub, M.: Arch. f. Augenh. **26**:336, 1892-1893.

eye, whereas a marked decrease of hyperopia takes place in the nonstrabismic eye right after the seventh year.

4. The rate of decrease of the hyperopia is much slower in the strabismic eye, being 10 per cent a year when the decrease is most marked, i. e., from 12 through 15 years of age, whereas in the nonstrabismic eye it is over 20 per cent per year when highest, i. e., from 8 through 11 years.

5. In keeping with my earlier findings and those of my former associates, Kronfeld and Bothman, at the University of Chicago, the average eye is found to become more and more hyperopic up to the age of 6 or 7, not less and less so, as widely held. The nonstrabismic eye, here considered by itself for the first time, also shows increasing hyperopia up to the end of the seventh year.

122 South Michigan Avenue (3).

ADDITIONAL EXPERIENCES WITH TETRAETHYL PYROPHOSPHATE IN TREATMENT OF GLAUCOMA

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SINCE the introduction of tetraethyl pyrophosphate as a miotic substance for treatment of primary glaucoma by topical administration,[1] this drug has been employed in the treatment of several times as many patients as those described in the first report, and enough additional information has been obtained to warrant a follow-up note. Accordingly, a summary of experiences with a representative group of 60 cases is presented. The drug was administered, as described in the original paper,[2] only to patients whose intraocular pressure was unsatisfactorily controlled by pilocarpine or physostigmine in the customary doses. If, after an adequate trial, tetraethyl pyrophosphate proved ineffective, administration of this drug was discontinued. However, if tetraethyl pyrophosphate was effective, its administration was continued but was interrupted from time to time for comparative trials of other miotics. This was done with the thought that a new drug, such as tetraethyl pyrophosphate, should achieve a place in therapeutics only if it proves distinctly better in some way than other drugs which are already available. Accordingly, continuation of treatment of patients with tetraethyl pyrophosphate was determined solely on the basis of whether or not the use of this drug seemed to be most advantageous to the individual patient. In accordance with this policy, the administration of tetraethyl pyrophosphate was gradually discontinued in all but two of the 60 cases during a 1½ year period following the start of treatment. In approximately one half the cases employment of tetraethyl pyrophosphate was suspended within the first two months of treatment. The reasons for discontinuing the drug were as follows:

1. Failure to benefit the patient even at the outset with tetraethyl pyrophosphate was responsible for stopping the treatment in 14 cases. These failures largely accounted for the discontinuations during the first two weeks of treatment. In these cases other miotics were also inadequate and operation was usually required.

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1. Grant, W. M.: Miotic and Antiglaucomatous Activity of Tetraethyl Pyrophosphate in Human Eyes, Arch. Ophth. **39**:579-586 (May) 1948.

2. Tetraethyl pyrophosphate was employed as a 0.025 to 0.1 per cent solution in peanut oil instilled in the conjunctival sac by the drop two to four times a day.

2. Eventual failure to control the pressure occurred in 11 cases after periods of successful treatment varying from two weeks to one and a half years. It is noteworthy that in these cases adequate control was not obtained with other miotics either, and recourse to surgical measures was usually necessary.

3. Use of tetraethyl pyrophosphate was no longer considered especially advantageous to the patient in 16 cases. After a trial period with the drug of one to nine months, equally good control of the pressure was obtained with other miotics, such as diisopropyl fluorophosphate, or with increased doses of pilocarpine and physostigmine plus methacholine (mecholyl®) or with some other type of drug.

4. Local sensitivity reactions occurred in six cases; these came on two weeks to six months after the start of treatment with tetraethyl

Comparison of Effectiveness of Tetraethyl Pyrophosphate (T. E. P.) with Other Miotics in Controlling the Intraocular Pressure in Primary Glaucoma *

	A	B	C	D	
		0.5% Physostigmine Salicylate Plus 20% Methacholine Chloride, t. i. d.	A Plus B	0.1% Diisopropyl Fluorophosphate (DFP)	
Tetraethyl Pyrophosphate	4% Pilocarpine Hydrochloride, q. i. d.			I. d.	B. i. d.
0.025% t. i. d.	++	+	..	= =	..
0.05% b. i. d.	+++++, = = = =	+	= =	= = =	..
0.05% t. i. d.	+++++	+	=	= =	..
0.1% b. i. d.	+++++	+	..	..	= = =
0.1% t. i. d.	+++	+	= =	..	= = =

* + indicates that tetraethyl pyrophosphate was more effective; = indicates that tetraethyl pyrophosphate was equally effective. One symbol is used for each case in which comparison was made.

pyrophosphate. This response resembled in all respects the acute sensitivity reactions which are produced by a number of other drugs applied to the eye, such as atropine, with redness and edema of the lids and eosinophils in the conjunctival secretions. The tetraethyl pyrophosphate itself, rather than the peanut oil vehicle, was identified as the sensitizing agent in these cases. No cross sensitization with diisopropyl fluorophosphate was found.

5. A variety of unrelated causes, such as death or irresponsibility in following any kind of treatment, was responsible for discontinuing tetraethyl pyrophosphate in nine cases. Inability to tolerate the drug because of blurring of vision from spasm of accommodation prevented further use in two cases.

Comparisons of tetraethyl pyrophosphate with pilocarpine, physostigmine and methacholine, and diisopropyl fluorophosphate in controlling the pressure at various dose levels is summarized in the accompanying table. As noted in the original report, tetraethyl pyro-

phosphate was generally more effective than pilocarpine in the usual doses. The impression obtained in comparing tetraethyl pyrophosphate with diisopropyl fluorophosphate was that the dosage of the shorter-acting tetraethyl pyrophosphate was more easily regulated with regard to the patient's comfort than was that of diisopropyl fluorophosphate, but that there was no fundamental difference between these two drugs in effectiveness in controlling pressure. Also, except for the sensitization phenomenon, no difference in toxicity was noted. Neither compound was observed to produce systemic intoxication from use in the eye.

A practical disadvantage which was found to be common to both tetraethyl pyrophosphate and diisopropyl fluorophosphate was their susceptibility to decomposition by water. In several instances sudden apparent loss of control of pressure was found to be attributable to the patient's inadvertent contamination of the oily solutions of these drugs with water, probably by transfer of tears on the medicine dropper or by washing the dropper with water. The presence of water could be easily detected in some instances by the milky or turbid appearance, due to emulsification of water droplets.

SUMMARY AND CONCLUSION

In a representative group of 60 cases of primary glaucoma in which the pressure was not adequately controlled by pilocarpine and physostigmine, tetraethyl pyrophosphate was frequently more effective. However, administration of tetraethyl pyrophosphate to the patients was gradually discontinued over a one and a half year period for the following principal reasons: In 25 cases miotic therapy was, or became, ineffective; in 16 cases other miotics, especially diisopropyl fluorophosphate, were found to be equally effective, and in 6 cases local sensitivity to tetraethyl pyrophosphate developed. It appears that in controlling the intraocular pressure in glaucoma tetraethyl pyrophosphate is comparable in effectiveness with other strong miotics, but that it offers no outstanding advantages and has the disadvantage of a considerable tendency to induce local sensitization. Also, in common with diisopropyl fluorophosphate, tetraethyl pyrophosphate is susceptible to decomposition by contamination with water.

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DISTANCE DISCRIMINATION

VII. Influence of Initial Position of Rods in Howard-Dolman Test *

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IN THE Howard-Dolman test of distance discrimination the administrator places the movable rod at some distance either nearer to or farther from the subject than the stationary rod before the subject attempts to aline the rods. This position of the movable rod in relation to the stationary rod is termed an initial position setting. The measure of the subject's distance discrimination is, of course, based on his errors in alining the rods. Because the initial position setting is a fundamental factor in the procedure, the validity of the examination depends on the assurance that the settings exert no significant influence on the subject's errors of alinement. Our observations in administering the Howard-Dolman test, however, have suggested the possibility of such an influence. The purpose of this investigation is to ascertain its presence or absence and to consider the nature of the influence if it does exist.

EXPERIMENT 1

Method.—The Howard-Dolman apparatus and procedure have been described in a previous paper (Weymouth and Hirsch, 1945). In the present study of the initial position setting, 100 binocular readings were taken by a subject, using the following 10 initial position settings arranged in this random order: + 100, 0, + 400, — 400, — 200, 0, — 300, + 300, + 200, — 100 (in millimeters). The cycle of settings was repeated until the 100 readings were obtained.

Results.—In the case of one initial setting the fact that an influence was exerted on the readings was immediately apparent. In 75 per cent (15 of 20) of the readings made with the zero setting, the subject stated that he believed the rods to be already alined and did not change the position of the movable rod. In addition, in the remainder of the trials with the zero setting the same statement was made by the subject, although he changed the position of the rod in an effort to confirm his

* Other papers in this series are listed in the bibliography.

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observation. It is apparent from the above that this particular initial position setting has a definite influence on the readings made by this subject. With its use a test of the subject's distance discrimination acuity as measured by his ability to aline the rods may be biased.

If there is exerted no significant influence on the readings by the initial position settings other than zero, the means of the groups of readings made on each of the remaining eight settings should not differ significantly from one another. To determine the significance of the difference, a hypothesis of no significant difference among the means, a null hypothesis, was postulated. The hypothesis was to be tested by analysis of variance after a determination of the homogeneity of the data by Bartlett's test; however, calculation produced a chi-square value of 41.41, with a probability value of less than 0.01 (7 degrees of freedom), indicating nonhomogeneous data and rendering further calculation valueless. To test the significance of the influence of the settings other than zero further data were required.

EXPERIMENT 2

Eighty readings were made by each of eight subjects using the before-mentioned series of initial position settings, exclusive of the zero settings. Homogeneity values for the eight sets of data thus obtained were calculated preparatory to testing the significance of the difference among the means of the readings made on the various settings, as described in experiment 1. Several of the sets failed to satisfy Bartlett's test, a fact which suggested either a somewhat general lack of acuteness among the subjects in the alinements or, more probably, the existence of some factor in the examination which altered the acuteness of response (i. e., the position of subjective equality) of the subjects during the testing. Graphing the cumulative sums of the readings against the numbers of the readings provides a ready demonstration of variations in the position of subjective equality (abbreviated E_s) during the examination. Any change in the slope of the curve resulting from data graphed in this manner indicates a change in the E_s. The sets of data were graphed in the manner described and the curves examined. In every graph the first few points were erratic and in no case fell on the curves that were described by the remainder of the data. This general tendency was ascribed to a learning or accustoming process with the apparatus on the part of the subjects. These initial values were, therefore, considered a false indication of the E_s of the subjects, and, since all variations in the initial values occurred within the first eight readings, the first cycle of eight values (the first reading taken with each of the settings) was discarded and Bartlett's test made on the remaining 72 readings for each of the eight sets of data. Taking as an indication of

homogeneity any P value above 0.05, we found that seven of the eight sets of data satisfied Bartlett's test (table).

As in the preliminary experiment, the null hypothesis of no significant difference among the group means was postulated, and the hypothesis was tested by analysis of variance for the eight sets of data. Four of the variance ratio values calculated were not significant at either the 5 or the 1 per cent levels (subjects 1, 4, 6 and 8, table). Consequently, these four sets of data bear out the null hypothesis and, therefore, the absence of any significant influence of the initial position settings on the readings of these four subjects. In the case of subject 2 a variance ratio value significant at the 1 per cent level was obtained from the data; however, the ratio was inverted; i. e., the mean square, or variance, of the groups was smaller than the mean square of the

Statistical Values from Data of Eight Subjects

Subject No.	Homogeneity Value	Approximate Homogeneity Probability Value (7 df.)*	Variance Ratio (F)	Variance Ratio Level of Significance (7/64 df.)	Sensitivity (Standard Deviation)	Position of Subjective Equality (Mean of Total)
1	11.72	0.11	1.66	Below 5%	61.04	125.44
2	8.34	0.30	6.01†	Above 1%†	7.39	— 2.90
3	11.29	0.13	3.10	Above 1%	36.79	34.25
4	2.13	0.87	1.00	Below 5%	12.65	10.12
5	12.39	0.09	22.57	Above 1%	188.42	18.22
6	10.68	0.13	1.63	Below 5%	21.29	18.46
7	20.18	<0.01	....	.....	12.11	1.75
8	6.43	0.50	1.56	Below 5%	9.24	—31.06

* Inverted ratio.
† 64/7 df.

individuals within the groups. The inversion was considered a product of chance; and because such a ratio cannot be interpreted physiologically, it must be discounted.

The variance ratios of the two remaining sets of data (subjects 3 and 5), on the other hand, were both significant at the 1 per cent level, thereby denying the null hypothesis and indicating that the initial position settings did influence significantly the readings of these two subjects.

In order to determine how the influence of the settings on the readings manifested itself, i. e., how the readings varied with the settings, coefficients of correlation between readings and settings were calculated for the data of subjects 3 and 5, respectively. The value for the data of subject 3 was —0.404 (70 degrees of freedom), and that for the data of subject 5, +0.791. Both values are significant at the 1 per cent level, indicating a high correlation. It is interesting that in one case the

correlation was negative and in the other positive. In other words, the variation in the initial setting caused subject 5 to exaggerate his errors, i. e., to "shoot" beyond (in the cases of the plus settings) or short (with minus settings) of his normal position of subjective equality; it is also possible that the subject merely left the movable rod in the vicinity of the setting, a belief supported by the magnitude of the subject's errors. The variation caused subject 3 to overcompensate in alining the rods in the direction opposite that of the initial position setting, varying his E_s accordingly.

The data are too few for a satisfactory consideration of the influence of the settings on sensitivity. It may be noted, however, that the two subjects whose positions of subjective equality were significantly influenced by the initial settings had poorer sensitivities (higher total standard deviations) than the subjects whose data indicated no setting influence, with the exception of subject 1 (table). On the strength of these results it may be suggested that selection of subjects on a basis of low standard deviation would exclude those influenced by the initial settings.

SUMMARY

Our experiments on the significance of initial position settings in the Howard-Dolman procedure for testing binocular distance discrimination have demonstrated that the setting may have a significant influence on the errors of alinement of a subject. This influence may be manifested in three ways: It may cause the subject to exaggerate his errors in the direction of the setting (plus or minus), to leave the rod in the vicinity of the setting or to overcompensate for the setting by moving the aliming rod past his normal position of subjective equality in the direction opposite that of the setting. The errors of four of the eight subjects seemed to be unaffected by the settings.

The initial position setting of 0 may have a definite influence on the errors of alinement, in that with its use the subject may realize that the rods are already alined and make no further effort to aline them. With the use of the zero setting a test of the subject's distance discrimination acuity as measured by his ability to aline the rods may be biased, and therefore this setting was considered to exert a significant influence.

Because the two subjects whose positions of subjective equality were significantly influenced by the initial settings had poorer sensitivities (higher total standard deviations) than the subjects whose data indicated no setting influence (with the exception of one uninfluenced subject), it may be suggested that selection of subjects on a basis of low standard deviation would exclude those influenced by the initial settings.

Graphing the cumulative sums of the readings of a subject against the numbers of the readings has demonstrated that between five and

eight readings are required to accustom the subject to the apparatus. These initial readings cannot be considered a valid indication of the subject's distance discrimination acuity.

The demonstration of a possible influence on the position of subjective equality exerted by nine initial position settings (—400, —300, —200, —100, 0, +100, +200, +300, +400, in millimeters) recommends that the factor of initial position settings in the Howard-Dolman procedure be controlled if a valid measure of binocular distance discrimination acuity is to be obtained.

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II. Effect on Threshold of Lateral Separation of the Test Objects

III. Effect of Rod Width on Threshold

IV. Effect of Aniseikonic Lenses on Distance Discrimination

V. Effect of Motion and Distance of Targets on Monocular and Binocular Distance Discrimination

VI. Relationship of Visual Acuity of Distance Discrimination

VII. Influence of Initial Position of Rods in Howard-Dolman Test

VIII. Influence of Rod Brightness and Background Illumination in Howard-Dolman Test

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STUDIES ON THE CRYSTALLINE LENS

II. Synthesis of Glutathione in the Normal and Cataractous Rabbit Lens

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RELATIVELY little is known about the anabolic processes (synthesis) of various components of the lens, although many studies have been made on the breakdown of metabolites and a few on the net degradation of some of its structural elements. Studies on metabolism of the lens have been limited almost exclusively to catabolic reactions. To the authors' knowledge, this is the first quantitative study of synthesis of any lens component.

The significance of synthetic processes in normal tissue physiology has been established in recent years by Schoenheimer and associates.[1] By means of molecules labeled with different isotopes, these workers studied various separate and coupled chemical reactions occurring within tissues and evolved a new concept of "the dynamic state of body constituents." In a book by this title,[1] Schoenheimer pointed out that "all constituents of living matter whether functional or structural, of simple or complex constitution, are in a steady state of rapid flux." Moreover, in tissues a balance exists between the synthetic, or anabolic, processes and the degradative, or catabolic, processes. The regenerative reactions (synthesis) are enzymatic in nature and are coupled to other chemical reactions, such as oxidation or dephosphorylation. The degradative reactions, affecting large molecules, such as proteins and fats, are under the influence of lytic enzymes, which constantly degrade these molecules to their constituent fragments.

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This study was supported in part by the Eye Bank for Sight Restoration, Inc., New York, and the United States Atomic Energy Commission.

This paper is taken in part from a dissertation submitted by F. C. Merriam in partial fulfilment of the requirement for the degree of Doctor of Philosophy from Boston University.

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Anabolic and catabolic processes are in balance, and tissue remains essentially constant in composition. After injury or death of the tissue the synthetic processes may be retarded through interruption of the oxidative processes, and unbalanced degenerative reactions then lead to dissolution of unstable structural elements.

On the basis of this concept, which, incidentally, has substantially replaced the older view that structural elements of tissue once formed are primarily in a fixed or stable state, the major structural element in the lens, viz., protein, is continuously being synthesized from polypeptides, which, in turn, are being formed from amino acids. Degenerative processes are hydrolyzing protein to polypeptides, and these are split into amino acids, all at rates approximately the same as those governing synthesis, so that (referring only to the adult lens) the concentrations of protein, polypeptides and amino acids remain essentially constant. New amino acids are entering the lens from aqueous humor and mixing with the pool of amino acids already present, while acids in the pool are lost to aqueous humor. Since regenerative reactions require energy, synthesis of polypeptides, and finally protein, must be coupled with exothermic reactions, such as oxidation of glucose. Other structural and functional elements in the lens, for example, fats, polysaccharides, and enzymes (also proteins), likewise undergo continuous reactions.

It is an impelling question to ask what part abnormalities in synthesis and degradation play in the formation of cataract.

Experimental proof for any synthetic reactions (except possibly synthesis of ascorbic acid, for which evidence is inconclusive) has been lacking in the case of the lens. The present paper is the first of several designed to supply information on the dynamic state of various constituents of the lens.

The constituent of the lens chosen for the first study was glutathione. This substance is composed of three amino acids, aminoacetic acid (glycine), glutamic acid and cysteine. Glutathione was selected because it is a polypeptide, and therefore information concerning its chemical reactivity in the lens may be useful in later studies involving proteins, and because the decreased concentration of glutathione in cataractous lenses is well known, from which it may be thought that this substance plays some role in maintaining transparency of the lens. The choice was also influenced by the availability of isotopic aminoacetic acid, which made it possible to investigate that part of the synthesis and degradation of glutathione concerned with the aminoacetic acid–peptide link. Aminoacetic acid, incidentally, could be estimated chemically and readily separated from glutathione.

The present study was designed to provide answers to the following questions:

1. Is glutathione synthesized by the lens, or does it enter the lens preformed from the aqueous humor?

2. What is the rate of synthesis of glutathione?

3. Is the lowered concentration of glutathione found in cataractous lenses caused by a decrease in the rate of synthesis or by an increase in the rate of destruction?

MATERIALS AND METHODS

Naphthalene cataracts were produced in rabbits by Dr. William Buschke, of the Ayer Laboratory at the Manhattan Eye, Ear and Throat Hospital, by feeding 2 to 4 Gm. of naphthalene daily over the course of about five days.

Rabbit lenses were cultured by the method of Merriam and Kinsey.[2] The synthetic culture medium (solution 1[2]), which contained electrolytes and dextrose, was fortified with 2 mg. per 100 ml. of aminoacetic acid labeled with C^{14} in either the methyl or the carboxyl position. The latter was prepared from barium carbonate by Dr. Robert Loftfield,[3] of the Huntington Memorial Laboratory, Harvard Medical School. The specific activity of C^{14} in the barium carbonate was 2.5 per cent, and that in the carboxyl position of the aminoacetic acid was 1.25 per cent. The aminoacetic acid had an activity of 1 millicurie of C^{14} per millimole. Aminoacetic acid labeled with C^{14} in the methyl position was obtained commercially.[4] This aminoacetic acid also had an activity of 1 millicurie per millimole.

Aminoacetic acid was determined by the method of Alexander and associates,[5] modified for very small quantities by Christensen.[6] The method consists in oxidizing aminoacetic acid to formaldehyde, carbon dioxide and ammonia with triketohydrindene hydrate (ninhydrin®) and simultaneously distilling the formaldehyde from the mixture with steam. The formaldehyde is then determined colorimetrically with chromotropic acid (4,5-dihydroxy-2,7-naphthalenedisulfonic acid) in sulfuric acid solution. Glutathione was determined by the usual iodometric titration procedure, which must include a correction for ascorbic acid. The latter was determined by titration with 2,6-dichlorobenzeneoneindophenol.

Glutathione was isolated from the lens in pure form by the following procedure: A lens was ground for one to two minutes in a glass mortar with 6.0 ml. of 1 per cent aqueous solution of trinitrophenol N. F. The mixture, along with several washes, containing a total of 4.0 ml. of the trinitrophenol, was transferred to a plastic centrifuge tube, allowed to stand for 10 minutes and finally centrifuged for 15 minutes at 3,000 rpm. The supernatant fluid was decanted into a 10 ml. volumetric flask and made up to volume with 1 per cent trinitrophenol. About 6 mg. of glutathione was added to 5 ml. of this solution to act as a carrier.

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2. Merriam, F. C., and Kinsey, V. E.: Studies on the Crystalline Lens: I. Technic for in Vitro Culture of Crystalline Lenses and Observations on Metabolism of the Lens, Arch. Ophth. **43**:979-988 (June) 1950.

3. Loftfield, R. B.: Preparation of C^{14}-Labeled Hydrogen Cyanide, Alanine, and Glycine, Nucleonics **1**:54-57, 1947.

4. From Tracerlab, Inc., Boston.

5. Alexander, B.; Landwehr, G., and Seligman, A. M.: Specific Micromethod for Colorimetric Determination of Glycine in Blood and Urine, J. Biol. Chem. **160**:51-59, 1945.

6. Christensen, H. N.: Personal communication to the authors.

The solution was placed in a 15 ml. centrifuge tube, and bromocresol green was added as an indicator. The following reagents were then added rapidly in order, with thorough mixing: 0.3 to 0.4 ml. of 0.6 N sodium hydroxide solution until the solution was almost neutral; 1.25 ml. of 7 per cent cadmium chloride; 1.0 ml. of molar sodium bicarbonate solution, and 0.1 to 0.2 ml. of 0.6 N sodium hydroxide solution. The alkali was added in two portions to prevent precipitation of gelatinous cadmium hydroxide. After standing for one hour in the refrigerator, the mixture was centrifuged, and the precipitate was washed three or four times with 5 ml. portions of distilled water. This procedure removed all soluble material containing C^{14}. The precipitate was then dissolved in 0.5 ml. of 2 N sulfuric acid solution, and the solution was diluted with 2.5 ml. of 0.5 N sulfuric acid to make a final volume of 3.0 ml. Aliquots of this aminoacetic acid-free solution were plated for direct counts. Recovery of added glutathione in control experiments carried through the above isolation procedure was 95 per cent.

The direct plating technic of Hogness[7] was employed for determining radioactivity of samples. Copper disks, 1 inch (2.5 cm.) in diameter, were oxidized in a Bunsen flame until the film on the disks assumed a blue-gray color in reflected light. When cool, the disks had a pink-gray color. Disks which became black were discarded, because aqueous solutions were liable to run over the edge. Aliquots of solutions were carefully delivered on the center of the disks with a special calibrated micropipet sealed to a 1 ml. pyrex® syringe. To prevent wetting, the outside of this syringe-micropipet was coated with silicone® stopcock grease. The tip was used to spread the solution uniformly over an area of about 2 sq. cm. on the center of the copper planchets. A manual sample changer, a thin window counter and an autoscaler® were used in counting samples.

Because of the softness of the radiations emitted by C^{14} it is necessary to correct the registered number of counts for self absorption of radiation from the sample. It is not necessary to compute the quantity of solid materials present in each of the various solutions used if the same volumes of reagents are used each time, since their concentrations do not vary appreciably from lens to lens. It was necessary, however, to determine the counting efficiency for each of the different solutions in which counts of radioactivity were to be made. This was done by determining the number of counts resulting from a known amount of labeled aminoacetic acid.

The aminoacetic acid was added to aliquots of the various solutions to be counted. The ratio of the number of counts recorded in the solutions to that obtained when an equal quantity of aminoacetic acid was added to distilled water represents the efficiency factor.

The following factors were obtained:

Culture medium	0.80
Aqueous trinitrophenol	0.95
Supernatant liquid from cadmium-glutathione precipitate	0.81
Acid cadmium-glutathione solution	0.65

These factors were used in calculating radioactivity in the various fractions investigated.

7. Hogness, J. R.; Roth, L. J.; Leifer, E., and Langham, W. H.: The Quantitative Determination of C^{14} Activity in Biological Systems by Direct Plating. J. Am. Chem. Soc. **70**:3840, 1948.

Calculation of the turnover rate of aminoacetic acid in glutathione was made on the basis of the following assumptions:

1. Diffusion of aminoacetic acid into the lens is a limiting factor for approximately the first six hours only, evidence for which is presented under "Results."

2. C^{14} incorporated into protein, or lost in carbon dioxide, was unavailable to participate in glutathione synthesis.

3. Only one C^{14} atom enters the glutathione molecule.

The rate of approach to isotopic equilibrium in glutathione, which gives a measure of the rate of synthesis, is expressed as the ratio of radioactivity per unit quantity of aminoacetic acid in glutathione at any given time, divided by radioactivity per unit quantity of aminoacetic acid in glutathione (or in the system) which would prevail at isotopic equilibrium. The radioactivity is conveniently expressed as counts per minute per microgram of aminoacetic acid.

The radioactivity of glutathione at any particular time is determined directly. The weight of aminoacetic acid is calculated from the quantity of glutathione present in the lens. The radioactivity per unit weight of aminoacetic acid in glutathione at equilibrium is dependent on the total number of aminoacetic acid molecules in the system which are free to dilute the added labeled aminoacetic acid. It is equal to the total radioactivity added (less that which is lost to protein and carbon dioxide) divided by the total aminoacetic acid in the system. This pool of aminoacetic acid is located in glutathione, in the lens as extractable aminoacetic acid and in the culture medium. The amount of aminoacetic acid in protein is disregarded (see assumption 2 above) because the rate of turnover is relatively low.

TABLE 1.—*Distribution of Radioactivity Following Incubation of Two Lenses with Aminoacetic Acid Labeled with C^{14}*

Sample	Aliquot		Number of Counts Made on Each Aliquot	Total Radioactivity, Counts/Min. × 10^{-4}	
	Number	Volume, Ml.		Lens 1*	Lens 7†
Culture medium initially	4	25.0	4,096	51.6	25.4
Culture medium at end of experiment	2	24.3	4,096	21.8	4.6
Lens extract	2	24.3	4,096	24.1	16.0
Supernatant fluid after precipitation of glutathione	2	24.3	512	3.3	2.4
Glutathione	2	24.3	4,096	2.0	5.0
Protein	2	25.3	1,024	2.4	1.5
Carbon dioxide	..	....	.....	0	3.0

* Lens 1 was incubated with $H_2NC^{14}H_2COOH$.
† Lens 7 was incubated with $H_2NCH_2C^{14}OOH$.

RESULTS

Fourteen normal lenses were incubated for various periods with radioactive aminoacetic acid, six with aminoacetic acid labeled with C^{14} in the methylene group and eight with aminoacetic acid labeled with C^{14} in the carboxyl group, and measurements were made of the amount of radioactive aminoacetic acid incorporated in various fractions of the lens.

Detailed results from typical experiments using the two types of labeled aminoacetic acid are presented in tables 1 and 2. The data show

that in both instances the radioactivity added in aminoacetic acid was incorporated into glutathione and, incidentally, also into protein.[8] The incorporation of aminoacetic acid in glutathione which has been replaced during the incubation period can be calculated readily from the data given in tables 1 and 2. The calculation for lens 1 follows.

The radioactivity in glutathione at the end of the culture period was 9×10^4 counts per minute. The glutathione in the lens contained 401 micrograms of aminoacetic acid; therefore, the radioactivity per unit quantity of aminoacetic acid was 224 counts per minute per microgram.

The radioactivity expected in glutathione at isotopic equilibrium is equal to the amount of labeled aminoacetic acid fed, less the amount lost to protein and carbon dioxide ($51.6 \times 10^4 - 2.4 \times 10^4 - 0$ counts per minute) divided by the weight of aminoacetic acid in the system (550 micrograms), or 895 counts per minute per microgram of aminoacetic acid.

The ratio of the radioactivity found at the end of 23.2 hours to that at equilibrium (224:895) is 0.251. Thus, 25.1 per cent of the aminoacetic acid in glutathione has been replaced with radioactive aminoacetic acid during this period.

TABLE 2.—*Distribution of Aminoacetic Acid in Various Fractions in Two Lens Culture Experiments*

	Incubation Time, Hr.	Weight of Lens, Mg.	Aminoacetic Acid Fed, Micrograms	Glutathione Aminoacetic Acid, Micrograms	Free Aminoacetic Acid, Micrograms	Total Aminoacetic Acid Pool, Micrograms
Lens 1	23.2	516	97	401	52	550
Lens 7	22.8	415	50	380	40	470

A turnover rate for aminoacetic acid in glutathione can be calculated from this value on the assumption that the reaction rate is proportional to the number of inert aminoacetic acid molecules in glutathione which are available to be replaced by radioactive aminoacetic acid, i. e., that the reaction is an exponential function of time and that it is not limited by some other factor. To determine the correctness of these assumptions, the percentage of unreacted aminoacetic acid for all of the experimental results was plotted on a logarithmic scale against the culture time, and the line which best represents the data was determined by inspection (chart). The deviation of the curve from a straight line indicates that initially there is some delay in the rate with which radioactive aminoacetic acid replaces inert aminoacetic acid in the glutathione. This delay is presumably caused by the rate with which radioactive aminoacetic acid diffuses into the lens. In any event, the average turnover rate of aminoacetic acid in glutathione may be calculated from the slope of the straight line portion of the curve. This rate is 2.38 per cent per hour. This means that half of the aminoacetic acid in glutathione is replaced by new aminoacetic acid every twenty-nine hours.

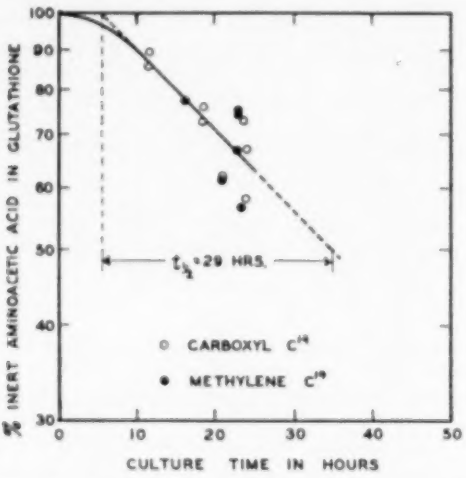
8. Footnote deleted by authors.

9. Synthesis of protein in the lens will be discussed in a subsequent paper.

Individual turnover rates may be computed from the slope of the line made by joining the experimental points to the point at which the line shown in the chart extrapolates to 100 per cent inert aminoacetic acid, viz., at six hours' culture time.

Table 3 shows the individual values for the turnover rate, the weight of the lens, the concentration of glutathione in each lens and the period of incubation.

Results obtained with lenses showing varying degrees of opacity as a result of feeding naphthalene are presented in table 4. The turnover rates for aminoacetic acid in glutathione were calculated in the same



Incorporation of aminoacetic acid in glutathione of normal rabbit lenses.

manner as were those for the normal lenses. Lenses A, B, C and D were cultured two days after the last feeding of naphthalene. Lenses A and B had mature cataracts, and about one tenth of the normal content of glutathione. The turnover rate of the aminoacetic acid in the glutathione of these lenses was about one fifth of normal. Lenses C and D were clear. Their glutathione contents, however, were reduced to about 60 per cent of normal. The turnover rates for aminoacetic acid in glutathione were slightly below normal.

Lenses E, F and G were cultured five days after the last feeding of naphthalene. Their glutathione contents were all decreased, and their turnover rates were considerably below normal. Lenses H and I

were taken from animals 12 days after the last feeding of naphthalene. In the case of lens H the glutathione content had not appreciably decreased. The lens showed only slight opacity, and the turnover rate was approximately normal. In the case of lens I the glutathione content was greatly reduced and the turnover rate was approximately normal.

TABLE 3.—*Turnover Rate of Glutathione in Normal Lenses*

Experiment No.*	Weight of Lens, Mg.	Glutathione Concentration, Mg./100 Gm.	Culture Time, Hr.	Incorporation Aminoacetic Acid in Glutathione, %	Turnover Rate of Glutathione, %/Hr.
1	516	348	23.2	25	1.08
2	502	330	16.0	20	2.56
3	525	340	23.2	23	1.53
4	300	421	21.0	38	3.14
5	342	404	23.8	44	3.14
6	353	344	23.2	33	2.30
7	415	371	23.8	27	1.77
8	419	409	24.0	33	2.22
9	427	390	24.0	47	3.00
10	394	398	11.6	14	2.76
11	430	365	11.8	11	2.03
12	347	404	18.5	27	2.46
13	343	421	18.5	24	2.22
14	322	370	21.0	39	3.14
				Average	2.35

* In experiments 1 through 6, lenses were incubated with $H_2NC^{14}H_2COOH$; in experiments 7 through 14, lenses were incubated with $H_2NCH_2C^{14}OOH$.

TABLE 4.—*Turnover Rate of Glutathione in Cataractous Lenses*

Lens	Weight of Lens, Mg.	Glutathione Concentration, Mg./100 Gm.	Culture Time, Hr.	Incorporation Aminoacetic Acid in Glutathione, %	Turnover Rate of Glutathione, %/Hr.	Time Since Last Naphthalene Feeding, Days
A	497	32	23.0	5	0.49	2
B	432	37	23.0	7	0.46	2
C	564	247	22.8	24	1.64	2
D	572	244	22.8	19	1.33	2
E	284	89	16.2	5	0.81	5
F	300	85	23.8	4	0.25	5
G	476	20	23.8	17	1.66	5
H	267	356	23.2	20	1.30	12
I	483	29	23.0	33	2.30	12
J	494	9	22.0	41	3.30	14

The same was true for lens J, which was removed from an animal 14 days after the last feeding of naphthalene.

COMMENT

The accuracy of computing the turnover rate of aminoacetic acid in glutathione was limited in several respects; for example, individual turnover rates for incorporation of aminoacetic acid in glutathione were calculated from the slope of the line made by joining the point representing the percentage of unreacted aminoacetic acid in glutathione at

the end of the culture period to the point obtained by extrapolating the best line that could be drawn through all the points to the line representing 100 per cent inert aminoacetic acid. In other words, an average value is used for the time at which the reaction of aminoacetic acid in glutathione is not limited by what we believe to be diffusion. The magnitude of the variability in turnover rates introduced by the necessity of using this method of approximation was estimated by assuming that the extrapolated point was in error by an hour in the case of a particular lens. The turnover rate so calculated differed by less than 10 per cent from the value obtained with the usual method of calculation.

Another factor which limited the accuracy with which the turnover rate could be calculated was the lack of information concerning the exact amount of aminoacetic acid in lens protein. Using the best available value for the probable quantity of aminoacetic acid present in protein, the effect of including the aminoacetic acid in the calculation in the case of one of the lenses was determined. This resulted in an increase in the turnover rate of aminoacetic acid in glutathione of less than 0.05 per cent per hour.

Thus, neither the necessity of making certain assumptions about the time at which diffusion is no longer limiting nor the disregard of the aminoacetic acid in protein appears to have introduced any significant difference in the calculated turnover rates, considering the variability observed in individual lenses.

The observation that C^{14} from aminoacetic acid was incorporated into glutathione, both when it was located in the carboxyl and when it was located in the methylene group, suggests that an intact aminoacetic acid molecule takes part in the reaction. Had only the C^{14} from the carboxyl-labeled aminoacetic acid been found in glutathione, incorporation of C^{14} might be thought to occur through carbon dioxide resulting from decarboxylation of the aminoacetic acid. Some decarboxylation does take place apparently, since approximately 10 per cent of C^{14} is recovered as carbon dioxide.

Lack of information concerning the turnover rate of glutamic acid or cysteine makes it difficult to decide whether turnover of aminoacetic acid in glutathione involves a total breakdown and resynthesis of the latter from its precursor amino acids or an exchange of aminoacetic acid molecules for those preexisting in an otherwise unchanged glutathione molecule.

Indirect evidence related to this problem, which is consistent with the "total synthesis" hypothesis, was cited by Rittenberg.[10] He found that the turnover rates of aminoacetic acid, leucine, tyrosine, lysine and

10. Rittenberg, D.: Isotope Technique and Metabolism of Glycine, Cold Spring Harbor Symp., Quant. Biol. **13**:173-179, 1948.

histidine in liver protein were approximately the same (viz., eight days). Since, on the basis of exchange, the rates would not be expected to bear any relation to one another, these data suggest that synthesis occurs in protein, and, by analogy, therefore, it presumably occurs in glutathione also.

The decrease in concentration of glutathione in the lens following naphthalene feeding seems more readily explicable on the basis of an inhibition of resynthesis, since inhibition of a simple exchange reaction would not be expected to cause a change in concentration unless one assumes further that the inhibition affects only the part of the reaction concerning the reformation of the peptide bond. In this event, the argument as to whether one is dealing with exchange or synthesis becomes one of definition.

At first sight it might be thought that the results obtained with lenses showing a reduced content of glutathione, i. e., those removed from rabbits fed naphthalene, could be accounted for entirely on the basis of an increase in the rate of degradation. That is, there is no need to postulate an inhibition of synthesis, whether it be based on an exchange or on a total resynthesis. While an increase in rate of destruction of glutathione will, in fact, reduce the concentration, it should be pointed out that an increase in the rate of degradation would not result in the large observed decrease in turnover time of aminoacetic acid in glutathione. Though the possibility of some increase in the rate of degradation cannot be ruled out, it may be concluded that the primary effect on glutathione is caused by an interference with the synthetic processes. It is not possible, however, to say whether the decreased rate of synthesis results from inhibition of enzymes directly concerned with synthesis or with those associated with the catabolic reactions which provide energy for the synthetic reactions.

From the results obtained with lenses taken from animals which had been on a normal diet for some days after naphthalene feeding, it is interesting to note that the glutathione remaining, even though greatly reduced in concentration, is degraded and glutathione is also resynthesized at approximately the normal rate. The data for lenses I and J support this view, although in both instances the amount of glutathione remaining was so low that the error in determining the turnover rate was much higher than when the concentration of glutathione in the lens is more nearly normal.

In conclusion, these studies indicate that glutathione is synthesized *in situ* by the lens and that impairment of the rate of synthesis, simultaneous with the formation of cataract, is primarily responsible for the decreased concentrations of this substance in opaque lenses resulting from feeding naphthalene to rabbits.

SUMMARY

Attention is called to the newer concept of metabolism which envisages all body constituents in a steady state of flux. The delicate balance existing in adult tissues between the synthetic and the degradative reactions maintains the structural elements constant in composition. When this balance is destroyed through a decrease in the rate of synthesis or an increase in the rate of degradation, dissolution of the unstable body elements occurs.

A study was made to determine whether in the lens, too, some of the constituents were rapidly being degraded and resynthesized from their constituent parts. Incorporation of aminoacetic acid (glycine) into lens glutathione and into lens protein was investigated by culturing lenses in a medium containing aminoacetic acid labeled with radioactive C^{14}. The average rate of turnover of aminoacetic acid in lens glutathione was 2.35 per cent per hour, and the turnover rate of aminoacetic acid in protein was of the same order of magnitude. These observations suggest that glutathione and protein in the lens are being continuously synthesized from their constituent amino acids.

The rates of turnover of glutathione in lenses removed from animals which were fed naphthalene were greatly decreased.

The reduced concentration of glutathione associated with the cataractogenic process was thought to result primarily from an inhibition of synthesis of glutathione, probably through poisoning of either the enzyme systems directly responsible for synthesis or those responsible for providing energy for the synthetic processes.

243 Charles Street.

MALIGNANT MELANOMA OF THE UVEAL TRACT

Report of Case with Death Thirty Years After Enucleation

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THE PRESENT case is of interest because of the extremely late postponement of death, a matter of some 30 years subsequent to initial enucleation for malignant melanoma of the eyeball. The case brings out a series of factors which appear to have considerable bearing on the apparent slowness of development of metastases and death. The case would suggest that the postoperative collapsed Tenon's capsule exerts a protective control of a residual optic nerve extension. Initial complications of glaucoma, rupture of the eyeball and probable necrosis of the initial neoplasm may have been important factors in the remarkable delay in the case.

REPORT OF CASE

History.—T. D., a man aged 59, entered the hospital complaining of neuritis of a week's duration, intermittent in character, involving the thigh. The pain was severer while he was lying in bed and appeared to recede on walking. Pain had also appeared in the small of the back about three weeks previously. His teeth were extracted on the advice of a physician, but, because of persistence of pain, he consulted a chiropractor, who informed him that a couple of vertebrae were out of place and that his right hip and shoulder were dropped. Treatments gave little relief, and admission to the hospital followed development of pains in the thigh.

The past history was irrelevant except that the patient reported that he had lost his left eye [1] 30 years before as a result of a kick from a mule. The mule

From the Department of Pathology, Missouri Baptist Hospital, St. Louis.

1. With regard to the time interval between the initial operation and the final hospitalization, the patient on several occasions gave the resident the history of losing his left eye 30 years previously, subsequent to an injury to his face. Because of the unusual interval noted, and because no one suspected the presence of a metastatic melanoma until its observation at autopsy, no attempt was made to go seriously into the details of the accident or the initial operation or of the operative and pathologic findings, prior to the death of the patient. Subsequent to autopsy, the staff surgeon obtained further information from the widow to the effect that her husband had been kicked under the jaw by a mule at least 25 years previously. There had been pain of about 10 days' duration over the left zygoma, which did not force him to stop work. About six months later his vision became cloudy and smoky; as a result, he consulted a number of eye and nerve specialists, who found nothing in his left eye. One nerve specialist said

(Footnote continued on next page)

had kicked him in the jaw and fractured his skull, and the nerve to the eye had been injured. He had also had "pleurisy pneumonia" about 10 years previously and had sustained an injury to his right leg 40 years before, for which he was hospitalized 13 days.

Physical Examination.—The head was of normal shape and size. The left eye was missing, and the right eye showed no conjunctival injection. The pupil reacted to light and in accommodation. There was no nasal discharge or obstruction. The septum was intact. All the teeth were missing. The tongue was not coated. The neck was free of abnormal vascular distentions or pulsations. The thyroid was not palpable, and no enlarged cervical lymph nodes were noted. The thorax was well developed. The respiratory movements were full, regular and equal on the two sides. Tactile fremitus was normal. The heart did not appear to be enlarged on percussion, and the apical impulse was not dispersed. No murmurs were present, and the rate and rhythm were normal. The resident noted that the liver was palpable 3 fingerbreadths below the costal margin and that there was an extension of liver dulness to this point. There was tenderness in the upper right abdominal quadrant. Pronounced kyphosis and right scoliosis of the spinal vertebrae were noted, and the right shoulder was carried higher than the left. The spinous processes of the twelfth thoracic and the first and second lumbar vertebrae were more prominent than normal. The upper extremities were essentially normal. There was an area of anesthesia over the ventral surface of the left thigh, middle third, measuring about 10 by 5 cm. This was bordered by a zone, 2 cm. in width, of partial anesthesia. The skin surfaces of the body were not remarkable. No moles were present.

Operation and Subsequent Course.—Operation was performed for a compression lesion of the spine of the first lumbar vertebra. A traumatic cause had not been completely excluded. Operation consisted of a laminectomy and two grafts of the thoracolumbar portion of the spine. At operation the cord did not appear to pulsate below the first lumbar segment until the laminas of the twelfth thoracic through to the fourth lumbar vertebrae were removed. The dura was not remarkable. The spinal fluid was clear.

After operation the patient in his fixation cast complained of pressure on the chest, oppression and shortness of breath and frequently attempted to sit up.

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that the change was due to his nerves but found nothing. About one year after the injury he suddenly became sick at his supper, vomited and had a headache. There was no pain in the eye, but he experienced severe pains across the frontal sinus, and the diagnosis of possible typhoid was made. He was sick for one week, and both eyes became swollen shut. He took morphine for relief, continuing its use for about a week. Then suddenly, at 1 o'clock in the morning, his left eye ruptured, and jellied, black to reddish contents appeared through the ruptured opening. An eye specialist was called and lanced the eye three times within a week. The pain became so severe that the patient asked for enucleation, which was performed at his home. The sight of the other eye was restored completely, and the patient had needed glasses for small print only in the past one or two years. His enucleation wound healed well, and he returned to work in 14 days. There was no subsequent pain in the head or in the socket. The diagnosis by the ophthalmic surgeon was "sarcoma." The patient had never had subsequent indigestion but had begun to tire in the last three years, although he had always been able to work. Within this three year period he had lost about 25 pounds (11.3 Kg.). At various times he had experienced "catches" in the back but had always got over them.

About twenty-four hours after termination of his operation, after an attempt to get propped up in bed, he suddenly began to choke. Collapse immediately followed, and death occurred in several minutes.

Report of Autopsy.—The body was that of a well developed, well nourished, middle-aged white man, exhibiting a very recent operative wound of the anterior surface of the left shin and of the thoracolumbar region of the spine. The left eye had been enucleated 30 years previously. The skin surfaces were otherwise intact. The heart lay intact in a smooth, glistening pericardial sac. The walls of the heart were well proportioned, but there were marked dilatation of the right side and firm contraction of the left. A large, massive and very recent thrombus of almost gel form, with proliferative deposits of plates of fibrin and platelets and showing lamination and coiling, was found lodged against the bifurcation of the pulmonary artery and was most prominent or lay chiefly, within the left branch. A small coiled element of recent antemortem thrombus was present in the right ventricle. The inferior vena cava contained broken antemortem thrombus at its point of passage through the diaphragm. When the vena cava was opened, a very recent antemortem gel clot was found located at a point corresponding to the orifice of the right renal vein, associated with slight roughening of the posterior caval endothelium. The vena cava as it approached the liver, immediately above the renal vein, was remarkably compressed by a huge tumor mass measuring 10 cm. in diameter, immediately beneath the liver capsule. Compression on the vena cava in the living subject must have been great, and it must have been completely occlusive on his bending forward. The aorta was smooth and in excellent condition. The lungs were peppered throughout with small, soft, grayish pink, sharply defined nodules, the largest measuring 1 cm. in diameter. The liver was smooth, glistening, brick red in color and moderately soft and weighed 2,870 Gm. (normal, about 1,800 Gm.). Its substance was dotted with numerous small nodules, measuring up to 10 cm. in diameter, as was that of the tumor which pressed on the vena cava. These tumors varied from dull, ochre red lesions, of semi-liquid consistency, to dark, soft masses, and one nodule consisted of jet black, pasty material, sharply defined and measuring 7 cm. in diameter. The major tumor mass was found to extend widely and wildly over the vena cava. The pancreas, gastro-intestinal system and kidneys were within normal limits, but several small nodules appeared in the medulla of one adrenal gland and the cortex of the other. The brain was carefully examined. All structures were normal. There was increased melanosis of the medulla and the upper segment of the spinal cord but no evidence of malignant involvement. No evidence of primary tumor formation or metastases was encountered in the brain. Extensive exploration was made of the floor of the cranial cavity, extending into the orbits. The right optic nerve measured 0.5 cm. in diameter and was essentially normal throughout. The right eyeball and orbit were clear, clean and intact. The left optic nerve averaged 0.2 cm. in diameter and terminated distally at a point which might have corresponded with the anterior terminus of the optic nerve at its point of contact with Tenon's capsule. The eyeball was absent, but at the aforementioned point at the terminus of the optic nerve an encapsulated tumor was embedded within the wrinkled enfolding, encapsulated scar of what was interpreted as a collapsed remnant of Tenon's capsule. Within this scar mass, the embedded tumor appeared unusually soft; it consisted of pale, pinkish gray to black tissue and measured approximately 0.7 by 0.9 by 0.5 cm. Hemisection of the lumbar vertebrae showed pronounced anterolateral hypertrophic osteoarthritis with suggestion of an old fracture and compression of the first lumbar vertebra. No neoplastic tissue was noted here.

Microscopic Studies.—Sections of the liver showed a marked compression effect, congestion and fibrosis, about a fibrotic, encapsulated mass which was centrally necrotic but contained tremendous amounts of dark brown material. Within the capsule this pigmented material was contained in short, spindle-shaped to polyhedral cells which were relatively undifferentiated but occasionally invaded thin-walled blood vessels. The pigment matter was completely intracellular. At other points there was observed a peculiar polyhedral cell with dark, eccentric nucleus, the latter showing variation in size and form. The nucleus frequently assumed a pyramidal to sickle form. Rare, delicate pseudocapillary vascular channels invaded this tumor. Rare spindle forms were present. In less cellular portions, neoplastic cells were arranged in palisade to frondlike or mesh or mesh forms. Mitotic figures were rare. A few of the latter cells contained only the previously noted brown pigment. Sections of the left optic nerve and of the encapsulated mass showed dense encapsulating bundles of fibrocollagenous tissue. These bundles intermittently covered and were involved by a central growth of polyhedral to spindle-shaped cells, which sometimes assumed a fibroblast form but exhibited dark, eccentric, frequently sickle-shaped nuclei. Some of these cells contained dark, sepia brown pigment matter. More superficially there was an area represented by a transitional, pseudostratified or even columnar type of epithelium. This shifted into a transitional type of growth with small pseudoacini. Stains for reticulum showed small, variable numbers of fibers in the tumor masses of both the optic nerve and the liver, particularly in the areas of spindle-shaped cell tissue. In the case of the optic nerve, there was evident complete degeneration and involution of nerve fiber tracts, while the peculiar encapsulating mass of dense fibrocollagenous tissue, which was distally infolded, was interpreted as the contracting remnants of Tenon's capsule. No neoplastic cells were identified in the proximal residual segments of the left optic nerve. The right eyeball and optic nerve were not remarkable. Melanotic masses were identified in the lung, the retroperitoneal lymph nodes and the adrenal glands. Microsections of the lumbar vertebrae showed aseptic central degeneration of the nucleus pulposus of the intervertebral disk above the involved first lumbar vertebra and aseptic necrosis of the bone graft.

It was felt that the postoperative immobilization of the patient in his cast, the pressure effect of the cast on the liver and the pressure of the enlarged liver and its major metastatic nodule on the subjacent vena cava resulted in a tremendous distention of the abdominal portion of the vena cava and the development of a thrombotic mass, which was suddenly swept away from its locus as a result of the patient's struggles and the subsequent propping up of his body, with actual elevation of the liver off the compressed vena cava. It is interesting that the staff surgeon attached no significance to the history of enucleation of the eye 30 years previously or to the enlargement of the liver reported by his resident.

COMMENT

Incidence.—Extensive statistics are given on the frequency of uveal melanomas. Griffith [2] reported an incidence of one choroidal sarcoma

2. Griffith, H., cited by Morris, W. F., and Oliver, C. A.: System of Diseases of the Eye, Philadelphia, J. B. Lippincott Company, 1897, vol. 3, p. 365.

per 3,000 pathologic eyes. According to Terry and Johns,[3] the condition occurs less frequently in the female and at a younger age, appearing in greatest numbers in the fifth decade, instead of the sixth, as for the male. Fuchs [4] reported 11 cases occurring in the first decade of life, while Terry and Johns,[3] in their summary of 94 cases, reported 7.4 per cent as allocated to the second decade of life, 10.6 per cent to the third, 14.9 per cent to the fourth, 21.3 per cent to the fifth, 22.3 per cent to the sixth and 4.3 per cent to the seventh, with the age unstated in 19.2 per cent. McKee,[5] of 42 patients, reported 17 to be 60 years of age or over. Weisner [6] reported a case of melanoma of the orbit in a 6 year old girl.

Etiology.—Trauma is frequently presented in the antecedent histories in many cases of melanoma. McKee [5] reported a definite history of trauma in five of his 42 cases. This was similarly noted in the present case. Ball and Lamb [7] reported a case in which the melanoma occurred 16 years after injury to the eye. Alexander [8] questioned the influence of injury and subsequent phthisis of the bulb on the subsequent development of this neoplasm. Leber and Krahnstöver [9] found only one of 200,000 cases of ophthalmic disease in which primary sarcoma occurred in an eye already atrophic from other causes and concluded that trauma and chronic inflammation were not predisposing factors. Meller [10] found one case of beginning sarcoma in an already atrophic eye among several hundred eyes studied histologically. Parsons [11] has shown, however, that proliferation of the retinal pigment epithelium is associated with chronic choroiditis. Initially these cells are round with oval nuclei and

3. Terry, T. L., and Johns, J. P.: Uveal Sarcoma—Malignant Melanoma: A Statistical Study of 94 Cases, Am. J. Ophth. **18**:903-913 (Oct.) 1935.

4. Fuchs, E., cited by Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 883.

5. McKee, S. H.: (*a*) Malignant Melanoma of the Uveal Tract, Arch. Ophth. **25**:238-242 (Feb.) 1941; (*b*) Primary Sarcoma of the Uveal Tract: An Analysis of 27 Cases, Canad. M. A. J. **36**:361-365, 1937.

6. Weisner, D. H.: A Case of Melanotic Sarcoma of the Orbit in a Girl 6 Years Old, Internat. J. Surgery **120**:385, 1889.

7. Ball, J. M., and Lamb, H. D.: Case of Epibulbar Melanotic Sarcoma, Occurring 16 Years After an Injury, Arch. Ophth. **52**:80-83 (Jan.) 1932.

8. Alexander, B.: The Pathology of Melanosis and of Benign Melanomas of the Ciliary Body, Arch. Ophth. **7**:521-537 (April) 1932.

9. Leber, T., and Krahnstöver, A.: Ueber die bei Aderhautsarkomen vorkommende Phthisis des Augapfels und über die Bedeutung von Verletzungen bei der Entstehung dieser Geschwülste, Arch. f. Ophth. **45**:164 and 231, 1898.

10. Meller, J.: Kleines Aderhautsarkom in einem nach perforierender Verletzung atrophisch gewesenen Auge, Centralbl. f. prakt. Augenh., July-August 1916, p. 108.

11. Parsons, J. H.: The Pathology of the Eye, London, Hodder & Stoughton, 1905, p. 449.

devoid of pigment and are actively ameboid.[12] They penetrate the stroma of the choroid and proliferate after the membrane of Bruch (lamina basalis) is broken. Subsequently, these cells exhibit strong potentialities of polymorphism, explaining the presence of increased numbers of typical spindle-shaped melanoblasts in the choroid or the ciliary body.

It has also been demonstrated[6] that cell damage and products of chronic inflammation can activate melanoblasts in overproduction of pigment with catalytic action in protein disintegration. This excess production of pigment occurs in the pigment epithelium of the iris, ciliary body and retina, as well as in melanotic tumors. This pigment appears to be a chemical irritant which further stimulates production of pigment and proliferation of melanoblasts[13] and results in chronic irritation both in the involved eye and in the companion eye. Alexander[6] expressed the strong belief that there is a relation between chronic inflammation and the formation of melanoma.

Glaucoma also appears peculiarly related to melanoma in a high percentage of cases of this tumor. Samuels[14] reported 15 cases of glaucoma among 31 cases of highly necrotic sarcoma in a series of 106 cases of sarcoma of the eye in the "Eno" laboratory of the New York Eye and Ear Infirmary, indicating also an especial association of glaucoma with necrotic development in the tumors. Terry and Johns[8] reported 33 cases of glaucoma in their series of 94 cases. Glaucoma was apparently a prominent complication in the present case.

Duration.—Terry[15] remarked that in his series he had no definite information as to the length of time it took tumors to reach the sizes noted at the time of enucleation. In some cases the patients had refused to permit enucleation immediately after the diagnosis was made and a separation of the retina had been observed several months before the eye was removed. In other cases the patients were sure their vision had been greatly below normal for a long time. It appeared certain that many of the tumors had grown relatively slowly and at such a rate that months, or even years, might elapse before the eye would become completely filled with the tumor. Terry expressed the belief that the rate of growth is often irregular but that it is impossible to state that all malignant melanomas grow slowly. Brown and Byars,[16] speaking

12. Krückmann, E.: Die pathologischen Veränderungen der retinalen Pigmentepithelzellen, Arch. f. Ophth. **48**:237, 1899.

13. Wietzing and Hundt: Melanin Pigmentierung, Beitr. z. path. Anat. u. z. allg. Path. **42**:23, 1907.

14. Samuels, B.: Anatomic and Clinical Manifestations of Necrosis in 84 Cases of Choroidal Sarcoma, Arch. Ophth. **11**:998-1027 (June) 1934.

15. Terry, T. L.: Malignant Melanoma—So-Called Sarcoma—of Uvea: II. Problems in Diagnosis, Arch. Ophth. **22**:989-1019 (Dec.) 1939.

16. Brown, J. B., and Byars, L. T.: Malignant Melanomas, with Report of 4 and 7 Year Cures, Surg., Gynec. & Obst. **71**:409-415 (Oct.) 1940.

of surface melanomas, reported that the local lesion may remain cured but that later, from a few months to 25 years, the patient may die of visceral metastases. These data do not appear to have been derived from the authors' own cases.

Diagnosis.—Moulton and Moulton [17] stated the belief that any tumor in the vitreous chamber of the human eye should be considered sarcoma until proved otherwise. Terry,[18] in differentiating melanoma and retinoblastoma, noted that sarcoma has been found in patients as late as the fourth decade and melanoma as early as the first decade of life. Thus, age is of no value in diagnosis. One may have to rely on the ophthalmoscopic appearance and on the presence of calcium (psammoma bodies), as shown by roentgenologic examination, in differentiating the retinoblastoma and the nonpigmented malignant melanoma invading the retina.

Source and Growth of Cells.—The inner layer of the optic cup in the developing eye differentiates into the neuroepithelial layer, while the other layer becomes the basal, or pigment epithelial, layer of the retina. Mann [18] stated the belief that this layer is again split into two layers by the ingrowing vascular tissue of the choroid, thus producing a layer of pigment on both the retinal and the scleral side of the choroid. The pigment cells first observed embryologically in the outer choroid layers would appear to be the outer epithelial layer, and from this choroidal pigment epithelium arises the malignant melanotic tumor of the choroid. Fuchs [4] traced early melanotic sarcoma to this layer, the retinal pigment epithelium remaining intact. Within the choroid two cell types are observed; one is a spindle-shaped or oval epithelial cell containing and producing within its substance the metabolic melanin. The second cell type is the chromatophore, a branched phagocytic cell containing pigment, which, however, has been produced and discharged from cells of the first type. Moore,[19] Usher [20] and Johnston [21] found benign melanosis to consist in massed collections of these chromatophores.

17. Moulton, H., and Moulton, E. C.: Sarcoma of the Choroid: History of 6 Cases, with Early Operation, J. A. M. A. **99**:460-462 (Aug. 6) 1932.

18. Mann, I. C.: Discussion on Intra- and Extra-Ocular Melanomata, Tr. Ophth. Soc. U. Kingdom **46**:132, 1926.

19. Moore, R. F.: Four Cases of Melanoma of the Choroid, with a Pathological Examination in One Case, and One Case of Unusual Chronicity, After Dissemination of a Melanotic Sarcoma Had Occurred, Roy. Lond. Ophth. Hosp. Rep. **19**:411, 1914.

20. Usher, C. H.: Melanoma of Choroid, Tr. Ophth. Soc. U. Kingdom **46**: 131, 1926.

21. Johnston, K. B.: The Ophthalmoscopic Picture of Naevus (Melanoma) Choroideae, Brit. J. Ophth. **13**:498 (Oct.) 1929.

Velhagen [22] noted that in benign melanosis these cells differ from normal pigment cells of the choroid, being spindle shaped with short processes or none at all.

De Schweinitz and Shumway,[23] Wolfrum,[24] Moore,[19] Heine,[25] Dawson [26] and Mulock Houwer [27] suggested the possibility of malignant transformation of a benign melanoma. None has given definite proof. Scheerer [28] stated that no such change has been observed. Wagener and Wellbrock [29] presented strong evidence of malignant change within a benign nonpigmented mole. This tumor almost duplicated one described by Velhagen [22] as *"kleinstes Sarkom."*

Murphy [30] stated the belief that a local neoplasm will not induce malignancy in adjacent normal cells, the tumor growth resulting solely from actual proliferation of tumor cells. Terry [5] then explained mixed tumors as the result of tumor arising from more than one cell type or of an attempt of extremely immature cells to differentiate into two or more mature related cell types. Study of the present case would suggest that an original tumor may be of low grade malignancy, changing later into a higher grade type of mixed form.

Classification of Types.—Callender and Wilder [31] have established two classifications of these melanomas, one according to the cell forms

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22. Velhagen, C.: Ein Melanoma und sogenannte kleinstes Sarkom der Chorioidea in demselben Augapfel, Klin. Monatsbl. f. Augenh. **80**:73, 1928.

23. de Schweinitz, G. E., and Shumway, E. A.: Concerning Melanoma of the Choroid, with Report of One Case of This Character and of Another Exhibiting a Pigmented Sarcoma of the Choroid Early in Its Development, Tr. Am. Ophth. Soc. **10**:439, 1905.

24. Wolfrum, M.: Der Naevus der Bindehaut des Augapfel und der Aderhaut und seine Beziehungen zu den melanotischen Tumoren, Arch. f. Ophth. **71**:195, 1909.

25. Heine, R. F.: Ueber Melanose und Sarkose des Augeninnern, Arch. f. Ophth. **111**:33, 1923.

26. Dawson, J. W.: The Melanomata: Their Morphology and Histogenesis, Edinburgh M. J. **32**:501 (Oct.) 1925.

27. Mulock Houwer, A. W.: Relation Between the So-Called Innocent Melanomata and the Malignant Tumours of the Choroid, Tr. Ophth. Soc. U. Kingdom **48**:167, 1928.

28. Scheerer, Richard: Melanosis choroideae, Ergebn. d. allg. Path. u. path. Anat. **21**:91, 1928.

29. Wagener, H. P., and Wellbrock, W. L. A.: Benign Melanoma and Melano-Epithelioma of the Choroid, Arch. Ophth. **4**:509-515 (Oct.) 1930.

30. Murphy, J. B.: Experimental Approach to Pre-Cancer Problem, Bull. Johns Hopkins Hosp. **56**:1, 1935.

31. Callender, G. R., and Wilder, H. C.: Melanoma of the Choroid, Am. J. Cancer **25**:251, 1935. Callender, G. R.: Malignant Melanotic Tumors of the Eye, Tr. Am. Acad. Ophth., 1931, p. 131. Wilder, H. C., and Callender, G. R.: Malignant Melanoma of the Choroid: Further Studies on Prognosis by Histologic Type and Fiber Content, Am. J. Ophth. **22**:851-855, 1939.

and the second according to the reticulum content, with variations in each type presenting different prognostic aspects.

1. Spindle Cell Type: In this type spindle-shaped cells with long oval nuclei appear in sheets, whorls and other irregular arrangements. The ends of the cells appear to terminate in fibers, so that the cells resemble fibroblasts. There is little argyrophil reticulum except that accompanying nutrient vessels. This cell type can be divided into two subtypes by their nuclear characteristics. Subtype A exhibits a delicate reticular structure of the nucleus with ill defined or indistinguishable nucleolus. Tumors of this cell type are usually heavily pigmented. Subtype B has a sharply defined, deeply stained, small round nucleolus, usually located near the center of the nucleus in a rather coarse nuclear network. Tumors of this cell type are usually lightly pigmented.

2. Fascicular Type: Cells of this type are elongated, sometimes forming fiber-like structures, but rounded and polygonal shapes may be seen. The typical nucleus is oval with distinct nucleolus and closely resembles the nucleus of spindle cell subtype B. Most of the cells are arranged in columns or fasciculi, the long axis of the cell being at right angles to that of the column. Cells radiate about the center of the column in palisade arrangement, the center being a lymphatic or a capillary blood vessel. Pigmentation is usually scant.

3. Epithelioid Type: This type is made up of polygonal cells, usually of relatively large size, although there is considerable variation in both size and shape. The nucleus is large, round or somewhat oval, and the nucleolus is distinct. Argyrophil reticulum is often rather abundant. The degree of pigmentation varies greatly.

4. Mixed Cell Type: There are irregular mixtures of spindle and epithelioid cell types with occasional fascicular forms. These are usually very heavily pigmented.

Local Growth, Extension, Recurrence and Metastasis.—Moore [32] pointed out that the tumor penetrates the vascular channels into the sclera and invades the soft tissues of the orbit. It follows the lymphatics and vascular spaces along the optic nerve and may appear within the cranial cavity. It ruptures through Bruch's membrane and fills the vitreous chamber. In terminal stages there are perforations at the sclerocorneal junction with the formation of a black, necrotic tumor on the anterior surface of the eye. Terry [33] cited 12 cases of invasion of the optic nerve in 94 cases of malignant melanoma. Terry demonstrated that malignant melanoma reaches the optic nerve from the choroid by extension along

32. Moore, R. A.: A Textbook of Pathology, Philadelphia and London, W. B. Saunders Company, 1944, pp. 1265-1267.

33. Terry, T. L.: Malignant Melanoma—So-Called Sarcoma—of Uvea: III. Extension into the Optic Nerve, Arch. Ophth. **24**:206-214 (July) 1940.

the retina, by direct extension into the optic nerve through the border tissue of the intraocular canal of the optic nerve and by metastases. He also suggested that the low invasion rate (10 to 13 per cent) would indicate that the optic nerve and the retina, especially the nerve fiber layer, are not "fertile soil." In two of Terry's cases of optic nerve invasion there was invasion of the cranial cavity along the optic nerve, destroying the chiasmal fibers and producing hemianopsia in the other eye. Byers and MacMillan [34] reported 40 extensions into the optic nerve in 392 cases. McKee [36] stated that orbital recurrence is rare. In his series of 27 cases of primary melanoma of the eye, orbital recurrence was noted in only two. Terry and Johns [5] had only one recurrence or local metastasis in a total of 31 metastases. Buller [35] encountered a case of melanotic fibrosarcoma of the orbit which was removed 10 years after the enucleation of an eyeball containing a pigmented growth. Moulton and Moulton [17] also emphasized the rarity of local recurrences even in the presence of multiple distal metastases. Terry was emphatic as to the importance of Tenon's capsule, stating that the contracted capsule after enucleation may be sufficiently dense and avascular to prevent the growth of a tumor localized distally in the residual optic stalk. It is also possible that Tenon's capsule may hold the tumor in check long enough at least for metastases already existent, or metastases from this orbital recurrence, to kill the patient before the local recurrence manifests itself. This mechanism appears to be clearly demonstrated in the present case.

Moulton and Moulton [17] pointed out the readiness with which metastases appear in very early optic sarcoma. Terry and Johns [5] indicated involvement of the cervical nodes by the lymphatics and of the brain by extension along or through the optic nerve. He stated the belief that all other metastases are blood borne. The liver is involved in 50 per cent of all metastases, but the exact reason for this is not known. It may be due to the special character of the blood channels, the sluggish blood current in the liver, a biochemical affinity or the absence of the "inhibitor material" of Murphy.[10]

Many instances are recorded of unusual delays in the appearance of metastases after initial enucleations. Ginsberg [36] noted metastases as late as 24 years after enucleation. Terry and Johns,[5] in a series of 94 cases, noted six cases in which metastasis occurred after five years and four cases in which it occurred between nine and twelve years after

34. Byers, W. G. M., and MacMillan, J. A.: Tr. Am. Ophth. Soc. **33**:184, 1935.

35. Buller, F.: Melanotic Fibrosarcoma of Orbit Removed Ten Years After Enucleation of the Eyeball Containing a Pigmented Growth, Am. J. Ophth. **2**:118-123, 1885.

36. Ginsberg: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1928, vol. 11, pt. 1, p. 515.

enucleation. He concluded, therefore, that the usual five year period is an insufficient interval in which to determine the malignancy of melanomas. Webb-Johnson and MacLeod [37] reported metastases 18 years after removal of the eyeball. Capt. E. De Coursey [38] reported a case of metastases 16 years after enucleation of the eye. In the original society communication, by typographic error, this interval was incorrectly given as 26 years. Both the American Registry of Pathology [39] and Terry and Johns,[3] in their separate series, showed no metastases arising in tumors of spindle cell subtype A. Both reports showed mixed cell types, giving rise to most metastases. De Coursey,[38a] however, showed metastases occurring in spindle cell subtype A tumors.

Prognosis.—Callender and Wilder [31] indicated from their statistics that the malignancy of the tumors appears to be inversely proportional to the degree of intercellular invasion by argyrophil fibers, and at the time of their original paper they reported that there had been no instances of death from melanomas of pure spindle cell subtype A or from tumors of the fascicular type in the classification based on the fiber content, and that the patient in every case in which no argyrophil fibers appeared among the tumor cells had died.

Cell Type	Percentage Dead Within Five Years
Spindle cell subtype A	0
Spindle cell subtype B	21
Fascicular	50
Epithelioid	80
Mixed	65

Fiber Content (reticulum)	Percentage Dead Within Five Years
No fibers	100
Less than 50%	58
About 50%	44
More than 50%	29
Fibers in all areas	0

De Coursey [38a] appears to have presented the first report before a scientific body of a death from an intraocular melanoma of the spindle cell subtype A variety, the nuclei of which do not present a conspicuous nucleolus. Also, for the first time, he reported a death from an intraocular melanoma with argyrophil fibers separating individual cells of the tumor, classified as heavily fibered. These deaths were from a series of

37. Webb-Johnson, A. E., and MacLeod, C. E. A.: Metastasis of Melanotic Cancer 18 Years After Removal of the Eyeball, Brit. M. J. **1**:314, 1924.

38. De Coursey, E.: (*a*) Proceedings of the Meeting of the American Association for the Study of Neoplastic Diseases, held at the Mayflower Hotel, Washington, D. C., September 7, 8 and 9, 1939; (*b*) Personal communication to the author.

39. American Registry of Pathology, Tr. Am. Acad. Ophth., 1934, p. 475.

350 eyes enucleated for melanoma in patients who had been followed for five years or longer in the Registry of Ophthalmic Pathology at the Army Medical Museum. Terry and Johns [8] also reported the prognosis in spindle subtypes A and B as good, but comparison of the prognosis on the histologic basis with the actual follow-up results shows that of 94 cases, a good prognosis was given erroneously in five cases and a bad prognosis in 14 cases. Of McKee's [9] 42 cases, typed according to the Callender classification, 14, or 30 per cent, were of the spindle cell subtype A and should have had, and actually did have, an excellent prognosis. In the remaining 26, or 70 per cent, a bad prognosis was verified. Of Moulton's [17] six early cases in three of which the patients died, two were of the round cell type and one of the spindle cell type. The three survivors, who were followed for 28½, 16 and 15 years, respectively, all had the spindle cell type. Of the three who died, one survived 19 years, before death from metastases. The authors stated that if a tumor is allowed to grow through the eyeball death is almost certain to follow, but that if the eyeball is removed before the outer coats are involved, recurrence and metastases are less likely.

Necrosis of the Tumor.—Samuels,[14] in an anatomic survey of 84 cases, demonstrated that no tissue within the globe can withstand the death-dealing toxins generated in the necrotic sarcoma. He stated the opinion that if a tumor is not suspected and an operation for relief of pain and high intraocular tension is performed, the opening of the globe may have a laudable aspect. The rapid diminution of pressure may cause rupture of the thin-walled vessels of the tumor and, with the extravasation of blood, induce acute necrosis, as seems to have occurred in several of his cases and in the case under discussion. As a consequence, symptoms become worse than they were before, necessitating enucleation without further delay.

Of his 84 uveal tumors, 20 were totally necrotic, representing a spontaneous local cure in 23.8 per cent. Fifteen tumors, or 16.6 per cent, had extensions into the orbital tissues. There was no indication that metastasis was ever discovered at the time of enucleation. Samuels [14] remarked on the duration of existence of local manifestations of uveal sarcoma and on the degenerative changes that may develop without clinical evidence of distant metastases or of transplantation.

Treatment.—Moulton and Moulton [17] stated that any tumor seen in the vitreous chamber should be considered malignant until proved otherwise and calls for enucleation. Terry and Johns [8] expressed the belief that the failure to remove an eye containing a malignant melanoma is a greater mistake than the removal of an eye erroneously thought to contain the neoplasm. Terry [15] also stated that hopelessly injured eyes and all painful blind eyes should be enucleated, as they may contain malignant

melanomas. He also stressed that whenever there is a possibility of a malignant melanoma every effort should be made to avoid performing an evisceration of the eye instead of an enucleation. Terry [40] also pointed out that if a long enough piece of optic nerve is removed at the time of initial enucleation, recurrence in the orbit or extension into the cranial cavity can often be prevented when the optic nerve is distally invaded by a malignant melanoma. This is not always possible, as the neoplasm may have extended along the nerve into the optic foramen before the enucleation. If there is clinical indication of involvement of the optic nerve confirmation by frozen section is easy and quick, and exenteration of the orbit should be done. As the initial section of the involved optic nerve may have spread viable tumor cells into other parts of the orbit, in the relatively healthy patient one should combine exenteration of the orbit with an exsection of the intracranial and interosseous portions of the optic nerve. If there is no neoplasm present in the optic nerve, then neurectomy can be performed close to the eye with safety. Again, the absence of tumor cells should be confirmed by frozen section. However, one can only stress the importance of removal of a long piece of nerve with the eye in any routine enucleation when it is noted that over 40 per cent of the intraocular malignant melanomas are not even suspected at the time of enucleation. Removal of long segments of nerve does not materially affect convalescence or the end results of enucleation. Use of clamps or hemostats on the nerve not only controls hemorrhage, as well as operative extrusion of malignant cells, but also facilitates the removal of a longer segment of nerve after freeing the globe. Würdemann [40] performed exenteration of the orbit for primary melanosarcoma of the eyelid, as well as of the orbit, one case in particular showing no recurrence five years later.

That the above method of handling these primary tumors is not universally accepted is pointed out in a remarkable paper by Lehrfeld,[41] who presented unusual and startling, if not erroneous, facts and conclusions. Lehrfeld asserted that early enucleation in a case of malignant melanoma that is confined to the eyeball is not a satisfactory surgical procedure in terms of life expectancy.

CONCLUSIONS

A case study is reported of death from metastases 30 years after initial enucleation for malignant melanoma of the uveal tract. This study illustrates certain factors:

40. Würdemann, H. V.: Primary Melanotic Sarcoma of the Lower Eyelid and Orbit; No Recurrence 5 Years After Removal and Exenteration of the Orbit, Ophthalmology **2**:38-40, 1905-1906.

41. Lehrfeld, L.: Is Enucleation Indicated in Early Cases of Intraocular Malignant Melanoma? Am. J. Ophth. **25**:199-202 (Feb.) 1942.

1. Exenteration of the orbit is necessary in case of uveal melanoma. It is felt that if this had been performed in the present case metastasis and death would not have occurred.

2. The size of the initial lesion is insignificant, the original melanoma in this case occurring as a persisting recurrence or extension within the collapsed folds of Tenon's capsule. The small size of the initial lesion contrasts greatly with the massiveness of the terminal distal metastases.

3. The major protective value of Tenon's capsule in enclosing within its collapsed folds and locally controlling the distal nerve extension is confirmed. In this case, a neoplasm remained some 30 years under control within the scar of Tenon's capsule, death occurring solely from a very late appearance of distal metastases.

4. Trauma again appears as an important etiologic factor in the development of uveal melanomas.

5. The initial complication of glaucoma, rupture of the eyeball and probable necrosis of the initial neoplasm may have been factors in the remarkable delay in this case. They were factors in necessitating early enucleation.

6. Death in this case came as a result of a non-neoplastic embolism arising from within the inferior vena cava, produced solely by a vascular pressure effect of a metastasis to the liver.

7. Histologic evaluation of the orbital recurrence and of the distal metastases indicated that a malignant form of neoplasm was developing in each tumor in a case in which the original growth had probably been less malignant. This suggests that in melanoma there may be a change in cell types and, with that, a change in characteristics of cell growth and in prognosis.

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INCREASED ACCURACY IN SQUINT SURGERY

Report of New Instrument

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THE OPERATION first described by Reese [1] in 1912, whether carried out as originally designed or with minor modifications, is still the most widely employed technic for shortening an extraocular muscle.[2] Yet the procedure, though based on sound surgical principles, does not always lead to entirely satisfactory results; this is mainly due to the difficulty of measuring with accuracy the amount of resection required. There exists, on the other hand, general agreement that extreme precision is of crucial importance in squint surgery.[3] Accordingly, a number of devices have been suggested by various authors, intended to determine with greater exactitude the correct place for insertion of sutures and resection of the muscle.

Separate calipers or strabismus rules have been designed by Walker, Jameson, Green and others. But instruments which are not part of the advancement forceps are awkward to use and liable to produce inaccurate measurements. Berens [4] attached a millimeter rule to the edge of a Prince advancement forceps. In handling this scale, however, it becomes necessary to grasp the muscle just beyond the line where the sutures are to be inserted, and the fibers are thus crushed in the very region which after resection is reattached to the muscle stump. It is to be remembered that Reese, in his original description of the operation,

1. Reese, R. G.: A New Muscle Resection Operation for Squint, New York M. J. **95**:60-62 (Jan. 13) 1912.

2. Wilkinson, O., and Wilkinson, R. W.: Strabismus—Its Etiology and Treatment, ed. 2, Boston, Meador Publishing Company, 1943, p. 287.

3. Wilkinson, O.: Present-Day Status of Squint Surgery: A New Operative Technique in Squint Surgery, J. A. M. A. **79**:1417-1422 (Oct. 21) 1922. Costenbader, F. D.: Causes of Failure in the Treatment of Squint, Am. J. Ophth. **28**: 1123-1132 (Oct.) 1945. Galeazzi, C.: Clinical Considerations and Specifications of Technic in the Surgical Treatment of Squint, Ann. ottal. e clin. ocul. **72**:506-508 (Aug.) 1946. Epstein, G. J.: Strabismus, Philadelphia, The Blakiston Company, 1948, p. 149. Wiener, M.: Surgery of the Eye, ed. 2, New York, Grune & Stratton, Inc., 1949, p. 330.

4. Lancaster, W. B.: Operations on the Ocular Muscles, in Berens, C.: The Eye and Its Diseases; Philadelphia, W. B. Saunders Company, 1936, chap. 65, p. 1138.

recommended placing the forceps as close as possible to the line of insertion of the muscle into the sclera. Spaeth [5] pointed out that only the portion of the tendon which is to be resected and discarded should be held in the grasp of the advancement forceps. Any damage to the part of the muscle used in subsequent reconstruction of the organ is decidedly detrimental.

The same objection can be raised against the George strabismus forceps described by Boynton.[6] This instrument has two pairs of serrated blades actuated by a threaded screw and adjusted to a millimeter scale on the handle of the fixed blade; in order to gage and control shortening of the muscle, both ends of the incised tendon are firmly grasped. But the device has the additional drawback that it actually consists of two forceps; the instrument is therefore bulky and unnecessarily obstructs the small operative field of squint surgery.

Nordlow [7] devised an instrument combining a millimeter-calibrated strabismus hook with a muscle fixation forceps arranged to permit the reading of measurements from the scale on the strabismus hook. The instrument is constructed so that the muscle hook fits into the lower part of the right-angled strabismus forceps, and by sliding the forceps along the hook it becomes possible to mark off a muscle segment of desired length. In practical use, however, Nordlow's instrument shows the same disadvantages as the two other devices mentioned above. The forceps is fixed to the distal portion of the muscle, thus crushing and injuring tissue which is to be reattached to the stump, and for that reason should remain intact in order to assure uncomplicated healing.

As it seemed possible to overcome the disadvantages inherent in the use of various types of strabismus forceps, attempts have been made from time to time to dispense with forceps altogether. It has been suggested that before severing the muscle sutures should be placed at the required distance and the intervening portion then excised. According to Yasuna,[8] a double-armed suture is placed in the under surface of the muscle close to its attachment to the sclera and 2 mm. from the muscle margin. Both arms of the suture are again passed through the muscle, the distance from the level of first insertion depending on the amount of resection planned. After the muscle is severed, the belly is pulled toward the stump, the sutures are tied and the superfluous

5. Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, ed. 4, Philadelphia, Lea & Febiger, 1948, p. 211.

6. Boynton, W. E.: Mechanical Exactness in Operating for Strabismus, Eye, Ear, Nose & Throat Monthly **6**:325-327 (July) 1927.

7. Nordlöw, W.: Instrument to Measure Muscle Resection in Strabismus Operations, Acta ophth. **22**:49-51, 1944.

8. Yasuna, E.: A Technique for Muscle Resection Without Use of the Prince Forceps, Am. J. Ophth. **31**:972-974 (Aug.) 1948.

tissue is excised. Similar methods have been described by Meller [9] and Török and Grout.[10] Accurate measurements, however, are still less likely with these procedures than by use of forceps, especially as it is difficult to insert sutures with the necessary minute exactness into the under surface of the muscle before it has been severed.

On the basis of these earlier experiences, it was felt that accuracy in squint surgery might be improved with the help of an instrument incorporating the following characteristics: 1. It should not be bulky and obscure the operative field. 2. The metric scale should be clearly visible and designed to be placed alongside the muscle at such an angle that the correct distance is easily established on the muscle surface and all objective causes of incorrect measurement are eliminated. 3. If the measuring device is to be attached to a strabismus forceps, the latter should remain securely in position once it has been clamped to the muscle; it should, furthermore, be possible to insert the sutures easily and with surgical accuracy at the desired site in the distal portion of

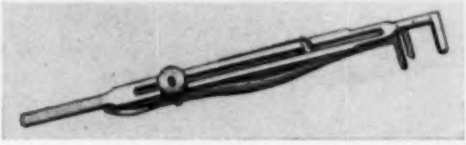

Fig. 1.—Diagrammatic drawing of the instrument, consisting of a right-angled advancement forceps to which a flat, calibrated sliding bar is attached.

the muscle. 4. The serrated jaws of the instrument should under no condition be clamped into the distal portion of the muscle where the sutures will be placed, as this practice would tend to jeopardize union of the tissues and prevent good healing.

In an attempt to fulfil all these prerequisites, a new instrument has been designed, consisting of an advancement forceps to which a flat, calibrated sliding bar is attached (fig. 1). The sliding scale is thin and flat and in intimate contact with the muscle forceps, taking up very little additional space. The jaws of the resection forceps form a right angle with the main body of the instrument, as does the cross arm of the sliding rule; thus measurements established along the scale can be accurately applied to the surface of the muscle. As the bar with the sliding rule can be attached to the forceps on either side, the instrument may be clamped to the muscle in any required position.

9. Meller, J.: Ophthalmic Surgery, Philadelphia, P. Blakiston's Son & Co., 1908, p. 87.

10. Török, E., and Grout, G. H.: Surgery of the Eye, ed. 2, Philadelphia, Lea & Febiger, 1925, p. 424.

The serrated jaws of the advancement forceps are fastened in the usual manner at the muscle attachment near the sclera. After the muscle has been severed, the proximal end of the rectus muscle with the forceps attached is well exposed by blunt dissection. The calibrated bar is then advanced to indicate the amount of resection required, measured from the edge of the jaws of the resection forceps to the cross arm, and is fastened in position by tightening the set screw (fig. 2). All sutures are placed at the distal edge of the cross arm of the sliding rule. Its proximal edge serves as a guide during resection and at the same time protects the sutures from being inadvertently cut.

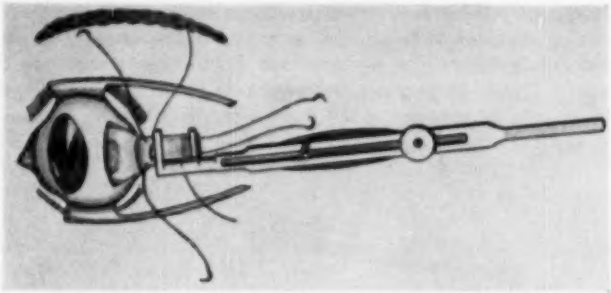

Fig. 2.—Diagrammatic drawing demonstrating use of the new instrument in strabismus resection. The muscle has been severed. The sliding bar has been advanced beyond the jaws of the forceps for a distance corresponding to the desired amount of resection. Sutures have been placed at the distal end of the cross arm of the sliding rule.

SUMMARY

An instrument is described, consisting of a right-angled advancement forceps to which a flat, calibrated sliding bar is attached. The exact amount of resection can be measured off on the scale moved beyond the jaws of the forceps. Obstruction of the operative field is avoided, and the new device neither interferes with the correct placing of sutures nor causes damage to the tissues of the muscle stump.

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EXPERIMENTAL INVESTIGATION OF PARACENTESIS IN THE TREATMENT OF OCULAR AMMONIA BURNS

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REPEATED paracentesis has frequently been proposed as a treatment for ammonia burns of the eye.[1] That such a treatment might be effective has been suggested by experimental and clinical indications that ammonia penetrates rapidly into the aqueous humor [2] and that damage of the iris and lens may result.[3] However, no substantial series of patients so treated has been presented, and the experimental evidence for the effectiveness of paracentesis appears to be limited to observations on three rabbit eyes which were reported to have benefited from this treatment in the hands of Siegrist [1b] in 1920. This evidence is quite inadequate in view of the relatively slight benefit reported and the considerable variations which are generally encountered in the responses of animals. Observations which have been made of the penetration and persistence of ammonia in the aqueous humor have been based principally on determinations of the ammonium ion without adequate consideration of the p_H of the aqueous humor, although it is the p_H which is probably the factor of prime significance. The ammonium ion per se has not been shown to be particularly toxic to the eye.

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1. (*a*) Pichler, A.: Ammoniak-Verätzung des Auges und der äusseren Haut, Ztschr. f. Augenh. **23**:297-321, 1910. (*b*) Siegrist, A.: Konzentrierte Alkali- und Säurewirkung auf das Auge, ibid. **43**:176-194, 1920. (*c*) Middleton, A. B.: Preparedness for Acid or Alkali Burns of the Eye, Illinois M. J. **67**:357-360, 1935. (*d*) Vail, D.: Discussion on Symposium on Ocular Injuries, J. A. M. A. **142**:253 and 255 (Jan. 28) 1949.

2. Pichler.[1a] Siegrist.[1b] Hoffmann, V.: Versuche zur Prüfung der Diffusionsgeschwindigkeit der Ammoniakflüssigkeit am Auge, Arch. f. Augenh. **91**:300-307, 1922.

3. Thies, O.: Ein Fall von schwerster Ammoniakverätzung mit doppelseitiger Bildung von Cataracta complicata und Ausgang in Erblindung, Klin. Monatsbl. f. Augenh. **72**:378-382, 1924. Teräskeli, H.: Schwere Ammoniakverätzung beider Augen, Acta ophth. **4**:274-277, 1927. Kiyosawa, M.: Die Verletzung des Auges durch Ammoniakgas, Acta Soc. ophth. Jap. **34**:1069-1074, 1930. Kiss, W.: Frühschädigung der Iris und Linse bei Ammoniakverätzung des Auges, Arch. f. Augenh. **110**:98-105, 1936.

In the present investigation additional evidence has been sought regarding the influence of paracentesis on experimental ammonia burns. In this study the influence of repeated rather than single paracentesis was investigated because it has been proposed from various sources that not only the early evacuation of the supposedly noxious aqueous humor but also the removal of reformed aqueous humor and reduction of intraocular pressure at a later stage was beneficial. Information has been obtained at the same time on the changes in the p_H of the aqueous humor which are associated with ammonia burns and on the tolerance of the eye to increased hydroxyl and ammonium ion concentrations in the aqueous humor.

EXPERIMENTAL STUDY

Experimental exposure of eyes to ammonia was performed in albino rabbits by holding the lids apart and instilling 3 to 4 drops of a concentrated solution of ammonia in water. The aqueous solution was employed rather than gaseous or liquid ammonia because of the greater convenience in handling. There is, of course, no fundamental difference in the mechanism of injury induced by the liquid and by the gas. Reagent grade ammonium hydroxide, containing 28.5 per cent ammonia and having a p_H of 13.2 as measured with the glass electrode, was employed. At the end of a period of exposure of from two to 20 seconds the principal excess of ammonia solution was flushed away by irrigation with a rapid stream of water for 10 seconds. Prior to exposure the rabbits were anesthetized by intravenous injection of 30 mg. of pentobarbital sodium per kilogram of body weight (average weight, 2 Kg.) and application of 1 drop of 0.5 per cent tetracaine hydrochloride to the eyes.

Paracentesis and removal of the whole aqueous humor was performed on one eye of each rabbit by means of a dry tuberculin syringe and a 27 gage needle at ½ to 45 minutes after exposure. A number of other eyes, mostly the fellow eyes in the same rabbits, which were exposed to ammonia in an identical manner but were not subjected to paracentesis, served as controls. The fluid which was withdrawn from the experimental eyes was immediately measured for degree of alkalinity by means of a glass electrode p_H meter.

Changes in p_H of the aqueous humor after exposure to ammonia were also made in dead rabbits in the same manner as that described for living animals in order to assess the effect of the blood circulation.

Subsequent treatment of the live rabbits consisted of daily cleansing of the conjunctival sacs of all eyes with water and paracentesis of the experimental eyes with a keratome daily until the fifth day after exposure, and then on alternate days until the tenth day. When possible, the keratome wound was simply reopened with a blunt instrument for the repeated paracenteses. Comparisons of the severity of the lesions in the two eyes of each animal were made by periodic biomicroscopic examination and estimation of the final degree of corneal opacification.

The relation of the elevation of the p_H of the fluid in the anterior chamber to its injuriousness to the eye was assessed by replacing the aqueous humor in normal rabbit eyes with 0.9 per cent sodium chloride solution to which ammonia had been added to attain various p_H values. In two rabbits the aqueous was simply withdrawn and replaced with the substitute solutions. In two other rabbits the anterior chambers were irrigated continuously for five minutes with the same solutions. The

toxicity of ammonium ions per se in the anterior chamber was assessed by withdrawing the aqueous humor from two normal rabbit eyes and replacing it with a neutral 1 per cent solution of ammonium chloride.

RESULTS

Two-second exposures of 12 eyes resulted in most instances in a permanent faint corneal nebula, with no significant difference between the six controls and the six eyes on which paracentesis was done at 1, 6 or 15 minutes after exposure. With this degree of exposure, nearly complete recovery was the usual result with or without paracentesis and in the same length of time. No cataracts were seen in these eyes.

Ten-second exposures of 10 eyes, half of which had paracentesis, caused severe reactions of the anterior segment with diffuse bluish

p_H of Aqueous Humor of Living and Dead Eyes After Three Periods of Exposure to Ammonia

	Average p_H of Aqueous Humor at Intervals After Exposure			
	Living Eyes			Dead Eyes
Time After Exposure, Min.	20 Seconds' Exposure	10 Seconds' Exposure	2 Seconds' Exposure	20 Seconds' Exposure
½	9.7	9.4	...	...
1	9.6	...	9.0	10.1
2	9.7	...	...	...
3½	9.8	...	...	10.0
6	9.2	9.4	8.7	...
15	9.0	8.7	7.8*	9.6
30	8.6	...	...	...
45	7.8*	...	...	...

*The p_H of the aqueous of normal rabbits was 7.6 by the same method of measurement.

swelling of the cornea, resulting in moderate persistent opacification and vascularization. The state of the eyes which were subjected to paracentesis was not improved over that of the controls at any time, and in two instances it was definitely inferior. Dissection of the eyes one month after exposure revealed no changes in the lenses.

Severe exposures for 20 seconds of 14 eyes, eight of which were treated with paracentesis, caused profound corneal opacification, vascularization and, not infrequently, perforation whether or not paracentesis was done at from ½ to 45 minutes after the exposure. Of the six control eyes, four showed dense corneal opacification and vascularization, with perforation in one of them, but moderate clearing with eventual visibility of the iris peripherally appeared in the other two eyes. None of the treated eyes showed significant clearing of the cornea.

The p_H of the aqueous humor which was removed from both living and dead eyes at various times after the three degrees of exposure are summarized in the table. In instances in which experiments were done

in quadruplicate, the average of the individual results is given. The average deviation of the individual measurements from the values in the table was only 0.15 p_H unit. In no instance was the alkalinity of the aqueous humor of living eyes found to reach p_H 10, although this value was attained in eyes of dead rabbits. The p_H of the aqueous humor returned spontaneously to essentially normal within 45 minutes after even the severest exposure and within 15 minutes after a moderate exposure.

In the experiment in which the aqueous humor of a rabbit eye was replaced with a 0.9 per cent sodium chloride solution to which sufficient ammonia had been added to raise the p_H to 11 there resulted intense corneal edema, chemosis, hyperemia of the iris and eventual extensive corneal opacification. However, when a solution at p_H 10 was employed, only moderate hyperemia of the iris and no permanent ocular damage was produced, either by simply replacing the aqueous humor with this solution or by irrigating the anterior chamber with it continuously for five minutes. A considerable resistance of the anterior chamber of the rabbit eye to damage by a solution of inorganic base at p_H 10 was, incidentally, also observed in experiments in which the anterior chamber was irrigated with solutions of calcium hydroxide and of sodium hydroxide at p_H 10 for five minutes and the fluid then allowed to remain there.

Replacement of the aqueous humor with 1 per cent neutral ammonium chloride solution in two instances caused considerable hyperemia of the iris; but by the next day the eyes appeared almost normal, and in another day they appeared completely normal. At this concentration of ammonium chloride it is probable that a far higher concentration of ammonium ion is reached in the anterior chamber than with even the severest exposures to ammonia. This estimation is based on the determination that in isotonic sodium chloride solution p_H 10 is attained by an ammonium hydroxide concentration of the order of 0.01 per cent. Investigation of the toxicity of ammonium ions at higher concentrations is complicated by the hypertonicity of the solutions, which introduces an independently damaging influence on the iris and lens. However, when a comparison is made of the toxicity of ammonium and sodium ions in neutral solution in the anterior chamber at nearly equivalent tonicities, but at concentrations far greater than those pertinent to the present study, i. e., in 10 per cent solutions, it is readily apparent that the sodium ion is much better tolerated than the ammonium ion.

COMMENT AND CONCLUSIONS

In the present investigation repeated paracentesis has been found to provide no significant benefit in a series of 19 rabbit eyes which were treated beginning ½ to 45 minutes after exposures to ammonia of three

degrees of severity. This experience differs from that of Siegrist,[1b] who provided the only previous experimental evidence on the subject. He exposed six rabbit eyes to an ammonia solution for ½ to one minute before irrigation and then performed paracentesis on four of the eyes. One of the eyes operated on had prolapse of the iris and hemorrhage and was considered eliminated from the experiment. The other eyes were examined only five days after exposure; at that time one of the two control eyes had diffuse corneal opacity with beginning vascularization, and the other had a completely opaque cornea, which perforated spontaneously. Of the three eyes successfully operated on, he found one to have only a slightly turbid cornea; another, pronounced turbidity of the cornea with an ulcer and hypopyon, and the third, a dense, gray-white opacification of the lower half of the cornea but only moderate opacity of the upper half. The subsequent courses were not described. These early observations were somewhat suggestive of an advantage from paracentesis; but since this apparent advantage has not been substantiated in the larger number of observations reported here, it appears that the original results are to be attributed to chance variation.

The measurements which have been made here of the change in p_H of the aqueous humor indicate, in agreement with the findings of other investigators,[2] most of whom have analyzed for ammonium ions, that ammonia gets into the aqueous humor within a matter of seconds. However, it appears from the measurements of p_H which have been made here, and from the results of the experiments in which the aqueous humor of normal eyes was replaced by an ammonia solution at p_H 10, that after exposure to ammonia the aqueous humor does not become sufficiently alkaline to be significantly injurious to the iris and lens, at least in rabbit eyes, even after an exposure which is devastating to the cornea. The attainment of only slightly higher p_H values for the aqueous humor of dead rabbit eyes than those for the living eyes suggests that limitation of the rise in the p_H of the aqueous humor in cases of ammonia burns is dependent in only small degree on vital processes, such as circulation of the blood or release of protein buffers into the aqueous humor.

The mechanism by which cataract and damage to the iris may be induced in human eyes by severe ammonia burns remains undetermined. These complications have been reported only in cases with extensive necrosis of the cornea and have usually become apparent during the second week after injury.

It seems quite certain that the ammonium ion itself is not responsible for a significant proportion of the damage to the eye in ammonia burns, for in the absence of abnormal hydroxyl ion concentration, as in the case of 1 per cent neutral ammonium chloride solution which was placed in the anterior chambers of rabbits, no special injurious action was observed

unless inordinately high concentrations of ammonium ion were tested. The ammonium ion has apparently been found clinically to have low toxicity for the anterior portion of the cornea by those who have recommended either ammonium chloride in 5 to 10 per cent solution for surface irrigation of chemically burned eyes [4] or solutions of other ammonium salts for treatment of lime burns. From experiments which have been noted in the present report, it may be concluded, however, that ammonium ions are not as well tolerated in the anterior chamber as are sodium ions.

There is no evidence at present to alter the assumption which is generally held that the injurious action of ammonia on the cornea is due simply to elevation of the p_H of this structure. The peculiarly rapid penetration of the cornea by ammonia is presumably due, in part at least, to a combination of water and lipid solubility, which facilitates passage of corneal barriers in a manner analogous to the facilitation of penetration of sulfur dioxide.[5]

Despite the rapidity of penetration of ammonia, no benefit has been shown to result from repeated paracentesis in adequately controlled experiments; accordingly, it seems improbable that benefit is to be expected from paracentesis following exposure to more slowly penetrating substances. The most effective treatment for chemical caustics appears still to consist simply of immediate copious irrigation with water.

SUMMARY

Repeated paracentesis of the cornea in 19 rabbit eyes beginning at ¼ to 45 minutes after exposure to ammonia of three degrees of severity resulted in no significant improvement at any time over the conditions in 17 control eyes. The p_H of the aqueous humor was elevated after exposure to ammonia, but it returned spontaneously to normal in 15 to 45 minutes and never reached appreciably damaging levels even with exposures which were devastating to the cornea. The ammonium ion per se did not appear to contribute significantly to the injury produced by exposure to ammonia. It is concluded that treatment of chemical burns of the eye by repeated paracentesis is not favored by the experimental evidence at present available.

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Miss Elizabeth O. Cushing assisted in performing these experiments.

4. Minton, J.: Occupational Eye Diseases and Injuries, New York, Grune & Stratton, Inc., 1949.

5. Grant, W. Morton: Ocular Injury Due to Sulfur Dioxide: II. Experimental Study and Comparison with Ocular Effects of Freezing, Arch. Ophth. **38**:762-774 (Dec.) 1947.

USE OF METHAPYRILENE (THENYLPYRAMINE) HYDROCHLORIDE IN OPHTHALMOLOGY

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METHAPYRILENE hydrochloride (thenylpyramine hydrochloride; N,N-dimethyl - N'[2 - thenyl] - N'-[2 - pyridyl] - ethylenediamine hydrochloride; histadyl®) is a derivative of ethylenediamine, which recently has been widely used by allergists for its antihistamine properties. During the past two years many reports have been published in the general medical literature dealing with its effectiveness in treatment of experimental and clinical hypersensitivities.

Landau and Gay [1] made a comparative study of antihistamine compounds, utilizing the Dale experiments. In these experiments the in vitro histamine neutralizing effects of nine common antihistamine compounds were tested. Methapyrilene hydrochloride was found to be one of the most potent of the histamine-competing agents. In later experiments these authors [2] tested the same nine compounds for their activity in vivo against histamine intoxication and anaphylactic shock in guinea pigs. They again found methapyrilene hydrochloride to be one of the most effective agents in protecting against histamine intoxication and anaphylactic shock. Subsequently, clinical reports have appeared by Gay and associates,[3] Feinberg and Bernstein,[4] Friedlaender and Friedlaender,[5] Kierland and Potter [6] and others. These studies have established the value of methapyrilene in the treatment of acute urticaria, allergic rhinitis, hay fever, serum sickness and food and drug allergies. Several of these authors, in addition, found that the systemic use of this drug in the treatment of allergic conditions with ocular complications resulted in prompt subsidence of the ocular symptoms.

Recently methapyrilene has been made available to ophthalmologists in the form of ophthalmic solutions and ophthalmic ointments. It is the

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From the McPherson Hospital.

Presented at the Ninth Clinical Meeting of the Wilmer Residents Association, April 20, 1950.

1. Landau, S. W., and Gay, L. N.: Bull. Johns Hopkins Hosp. **83**:330, 1948.
2. Landau, S. W.; Harriett, H. J. L., and Gay, L. N.: Bull. Johns Hopkins Hosp. **83**:343, 1948.
3. Gay, L. N., and others: Bull. Johns Hopkins Hosp. **83**:356, 1948.
4. Feinberg, S. M., and Bernstein, T. B.: J. Lab. & Clin. Med. **32**:1370, 1947.
5. Friedlaender, A. S., and Friedlaender, S.: Am. J. M. Sc. **215**:530, 1948.
6. Kierland, R., and Potter, R. T.: Am. J. M. Sc. **216**:20, 1948.

purpose of this paper to report the results in 120 patients who received this preparation locally in the treatment of diseases of the eye.

The methapyrilene used in treating these patients was in the form of a 0.5 per cent ophthalmic solution or a 0.5 per cent ophthalmic ointment. The patients were instructed to use 1 drop of the solution in either or both eyes three times during the day. The ointment was

TABLE 1.—*Results of Methapyrilene Therapy of External Diseases of the Eye Due to Hypersensitivity*

Condition	Complete Symptomatic Relief	Partial Symptomatic Relief	No Improvement	Total No.
Conjunctivitis in association with hay fever or asthma	21	..	2	23
Recurrent corneal erosion	5	2	..	7
Drug dermatitis of lids	17	..	1	18
Vernal conjunctivitis	8	2	..	10
Questionable allergic blepharoconjunctivitis without evidence of systemic hypersensitivity	5	..	..	5
Phlyctenular keratitis	1	..	..	1
Total	57	4	3	64

TABLE 2.—*Results of Methapyrilene Therapy of Ocular Diseases in Which Hypersensitivity May Be a Factor*

Condition	Complete Symptomatic Relief	Partial Symptomatic Relief	No Improvement	Total No.
Superficial punctate keratitis	7	1	9	17
(as part of penicillin reaction)	2	..	..	2
Chronic conjunctivitis	4	1	7	12
Marginal keratitis	1	1	3	5
Blepharitis	4	..	3	7
Episcleritis	2	1	1	4
Angioneurotic edema of lids	..	..	3	3
Nongranulomatous uveitis	1	1	2	4
Sterile corneal ulcer	..	2	..	2
Total	21	7	28	56

usually prescribed for use only at night or for topical application to the lids during the day. When systemic therapy was thought necessary, methapyrilene hydrochloride was prescribed in 25 mg. capsules, to be taken three times daily.[7]

RESULTS

The results are shown in tables 1 and 2.

7. The drugs used in this study were furnished through the courtesy of Eli Lilly and Company, Indianapolis 6. They market methapyrilene (thenylpyramine) hydrochloride under the trade name histadyl.®

Conjunctivitis Associated with Hay Fever or Asthma.—Twenty-three patients with conjunctivitis associated with hay fever or asthma received methapyrilene locally. Of this number, 21 experienced striking relief of symptoms while under treatment, and 2 were not relieved.

Recurrent Corneal Erosion.—Seven patients with the typical history and findings of recurrent corneal erosions were treated. All these patients received initially only local therapy with drops and ointment and were completely relieved. Treatment was stopped within seven days. Two patients experienced recurrences, and local treatment, when resumed, was supplemented with oral administration of 25 mg. of methapyrilene hydrochloride three times a day for one week. Both these patients were completely relieved and had no subsequent attacks.

Dermatitis of Lids Secondary to Drug Allergy.—Eighteen patients with dermatitis of the lids secondary to drug allergy received treatment. Seventeen of these patients experienced quick, complete relief of symptoms, with disappearance of itching and irritation within two days. Edema of the lids, as a rule, subsided completely within five days. For all patients use of the offending drug was immediately discontinued. One patient showed no substantial improvement in spite of additional systemic treatment.

Vernal Conjunctivitis.—Eight patients with vernal conjunctivitis were treated. Six patients had complete relief of local irritation and disappearance of the thick mucous discharge. Two patients were improved but continued to have itching. In none of these patients was there any improvement in the morphologic changes produced by prolonged vernal conjunctivitis other than some reduction in the edema of the retrotarsal folds.

Questionable Allergic Blepharoconjunctivitis Without Systemic Allergy.—Five patients with blepharoconjunctivitis whose histories and findings suggested local hypersensitivity as the etiologic factor in their disease were treated. All the patients were completely relieved by local treatment with methapyrilene solution, although no definite hypersensitivity could be demonstrated.

Phlyctenular Keratoconjunctivitis.—One patient with phlyctenular keratoconjunctivitis was treated with local use of both drops and ointment. This patient experienced immediate relief of his symptoms, and within forty-eight hours the limbal lesions disappeared entirely. Therapy was discontinued, and there has been no recurrence.

Superficial Punctate Keratitis.—Seventeen patients with superficial punctate keratitis for which no cause could be established received local treatment. Seven of these were completely relieved of symptoms; 1 was only partially relieved, and 9 experienced no improvement. The subsequent use of methapyrilene systemically by those patients who did not

respond did not effect any improvement. Two additional patients in whom superficial punctate keratitis developed as a part of a generalized reaction to penicillin experienced immediate subjective relief from the use of methapyrilene locally and systemically. Penicillin was withdrawn immediately.

Chronic Conjunctivitis.—Twelve patients with persistent chronic conjunctivitis were similarly treated. Most of these patients had received previous local treatment without prolonged relief from their symptoms. Four of these patients were completely relieved of their symptoms; 1 was partially relieved, and 7 were unimproved.

Marginal Keratitis.—Five patients with marginal keratitis of undetermined origin received local treatment. In 1 of these the condition cleared completely and has remained cleared; in 1 it was transiently relieved, and in 3 it was unchanged.

Marginal Blepharitis.—Seven patients with marginal blepharitis in association with moderate errors of refraction were treated. These patients all received methapyrilene ointment for topical application. Four were completely relieved, and the condition of 3 was unchanged.

Angioneurotic Edema of the Lids.—Three patients with angioneurotic edema of the lids received both local and systemic treatment with methapyrilene. In none of these patients was there any improvement.

Nongranulomatous Uveitis.—Four patients with acute nongranulomatous anterior uveitis were treated. In none of these patients could any etiologic agent be established. All of them received methapyrilene both locally and systemically. One patient showed dramatic clearing with no signs of activity after three days of treatment. One patient showed transient improvement, and the condition of 2 was completely unchanged.

Sterile Corneal Ulcer.—Two patients with corneal ulcers which were bacteriologically sterile received local treatment. Both showed transient improvement, but not definitive healing with this treatment.

COMPLICATIONS

Of the 120 patients who received methapyrilene locally, 7 complained of severe burning immediately after use of the drug, which persisted from three to five minutes. In 2 patients this sensation was so severe that medication had to be discontinued. Of the remainder of the patients, approximately one half stated, when questioned, that there was some transient stinging after use of the solution. Irritation was much less pronounced with use of the ointment than with use of the solution.

In 1 patient who received methapyrilene solution four times daily haziness of the corneal epithelium developed and persisted while she was receiving the medicament but disappeared when treatment ceased. This haziness recurred when treatment was resumed later, and treatment had to be discontinued.

Of the 25 patients who received systemic medication, none complained of any side effects, such as dizziness or drowsiness, although Gay and others reported an incidence of side effects ranging from 19 to 27 per cent.[8]

COMMENT

Randolph [9] has previously reported excellent results in the treatment of recurrent corneal erosion with systemic use of methapyrilene hydrochloride. In the present series, 5 of 7 patients treated responded to local therapy alone, the other 2 patients requiring further therapy with systemic administration of the drug.

The results of the present study in the treatment of external diseases of the eye which are of a frank hypersensitive nature parallel the results reported by Bourquin [10] and later by Hurwitz,[11] in treating similar disorders with antistine® (2-[*N*-phenyl-*N*-benzylaminomethyl]-imidazoline). Hurwitz, in a comparable series, found that 84 per cent of all patients treated experienced subjective relief. In the present series 64 patients of this type were treated (table 1); of these, 61, or 95 per cent, experienced complete or partial relief of symptoms, and only 3, or 5 per cent, were unimproved.

Fifty-six patients with disorders in which hypersensitivity might play a part were treated (table 2). Of these 56 patients, only 28, or 50 per cent, experienced any symptomatic relief. This result is probably not superior to that which might be obtained with other forms of local and systemic therapy. The possibility of combining antihistamine therapy with some more specific therapy in many of these cases should certainly be kept in mind. In many of them, methapyrilene might prove to be a valuable adjunct.

The good results obtained in treating disorders of a frank hypersensitive nature and the poorer results obtained in treating disorders in which hypersensitivity does not represent the direct etiologic agent indicate that methapyrilene hydrochloride has its greatest value in treating those disorders which are extraocular and represent frank hypersensitive states.

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8. Gay and others.[3] Feinberg and Bernstein.[6] Kierland and Potter.[5]

9. Randolph, M. Elliott: Paper presented at the Eighth Clinical Meeting, Wilmer Residents Association, 1949.

10. Bourquin, J. B.: Schweiz. med. Wchnschr. **76**:296, 1946.

11. Hurwitz, P.: Am. J. Ophth. **31**:1409, 1948.

SUMMARY

The results of treatment of 120 patients with various ocular diseases who received methapyrilene hydrochloride locally or systemically are reported.

Methapyrilene hydrochloride was found to be most effective in the treatment of extraocular disorders of a frank hypersensitive nature.

The commonest complication was found to be local irritation after the instillation of the ophthalmic solution. This occurred in 50 per cent of all patients treated, and in 2 patients it was so severe that treatment had to be stopped.

1110 West Main Street.

SURGICAL TREATMENT OF TUMORS OF THE OPTIC NERVE

Report of a Case

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AND
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THE REPORTED cases of primary tumor of the optic nerve now number over 400. Davis[1] has given an excellent review of the literature and discussed the pathology of gliomas of the optic nerve, with emphasis on the relation of these tumors to von Recklinghausen's neurofibromatosis. In this paper we wish to present a case of glioma of the optic nerve and emphasize the advantages of the newer surgical technics for dealing with these tumors.

The majority (at least two thirds) of optic nerve tumors are gliomas, and the remainder are meningiomas, with a few rare exceptions.[2] The gliomas occur predominantly in children, while meningiomas are commoner in adults and are, of course, not tumors of the optic nerve, strictly speaking. The tumors may involve only the intraorbital portion of the nerve or only the intracranial portion or both. The intraorbital neoplasms produce unilateral, painless exophthalmos and failing vision and are, therefore, manifest early and obviously. Optic nerve atrophy may or may not be present. Enlargement of the optic foramen, if present, is

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1. Davis, F. A.: Primary Tumors of the Optic Nerve (A Phenomenon of Recklinghausen's Disease): A Clinical and Pathologic Study with a Report of 5 Cases and a Review of the Literature, Arch. Ophth. **23**:735-821 (April); 957-1022 (May) 1940.

2. Echols, D. H.: Spongioblastoma Polare: A Clinicopathologic Study of 12 Cases, Arch. Neurol. & Psychiat. **39**:494-512 (March), 1938. Goldmann, H., and Grünthal, H.: Ueber einen Tumor des Sehnerven und seiner Leptomeningen bei Recklinghausenscher Krankheit, Ophthalmologica **102**:79-92, 1941. Reuling, F. H.: Glioma of the Optic Nerve, J. Iowa M. Soc. **33**:422-424, 1943. Verhoeff, F. H.: Primary Intraneural Tumors (Gliomas) of the Optic Nerve, Arch. Ophth. **51**:120-140 and 239-254, 1922. von Hippel, E., in von Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1925, vol. 7, pt. 2, pp. 535-574. Willemer, W.: Ueber eingentliche, d. h. sich innerhalb der äusseren Scheide entwickelnde Tumoren des Sehnerven, Arch. f. Ophth. **25**:161-247, 1879.

demonstrable on suitable roentgenograms and indicates intracranial extension of the tumor. However, intracranial extension may be present without this sign. A glioma confined to the intracranial portion of the optic nerve causes unilateral loss of vision, optic nerve atrophy and/or papilledema. If the tumor involves the chiasm, an atypical bitemporal hemianopsia may be present. Increased intracranial pressure and signs of pressure on adjacent cerebral structures develop late in the course of the tumor.

Primary optic nerve tumors have been attacked by surgeons since 1861 (Ritterich, cited by Martin and Cushing [3]). The usual approach has been through the orbit, with local excision of the tumor. This is perhaps natural, since these tumors were first operated on by ophthalmologists and continue to be regarded by many as a purely ophthalmologic problem. Several orbital approaches have been used: (1) through the conjunctivas with or without removal of the globe; (2) the Krönlein approach, through the lateral wall of the orbit; (3) the operation of Lagrange; (4) by incision through the eyebrow, and (5) through an infraorbital incision. Many ophthalmologists take special pains to preserve the globe.

In the early history of these intraorbital operations meningitis was a frequent complication, especially when the incision was made through the conjunctiva. Hudson [4] found the incidence of this serious complication to be 10 per cent. This incidence has probably been lowered by procedures such as those of Krönlein, Lagrange and Davis,[5] in which the incision is made through the skin, which can be sterilized.

However, the orbital approach has certain disadvantages. The exposure of the retrobulbar intraorbital contents is very limited with any purely orbital approach unless the bulb is removed. Very often it is impossible to determine whether the eye should be sacrificed until the lesion has been exposed and its nature ascertained. Jefferson and Hird [5] gave a good description of the difficulties encountered in trying to expose the optic nerve tumor by an orbital approach.

The principal disadvantage of the intraorbital approach is that it is never possible to expose and remove that portion of the optic nerve within the optic foramen and the intracranial cavity. Such exposure is important if the tumor is to be completely irradicated and if the mortality of these serious lesions is to be lowered. The nerve may be invaded posteriorly by neoplasm visible only by microscopic study.

3. Martin, P., and Cushing, H.: Primary Gliomas of the Chiasm and Optic Nerves in Their Intracranial Portion, Arch. Ophth. **52**:209-241, 1923.

4. Hudson, A. C.: Primary Tumours of the Optic Nerve, Roy. Lond. Ophth. Hosp. Rep. **18** (pt. 3): 317-439, 1912.

5. Hudson, A. C.; del Rio-Hortega; Wolff, B.; Jefferson, G.; Hird, B., and Neame, H.: Discussion on Tumours of the Optic Nerve, Proc. Roy. Soc. Med. **33**:685-692, 1940.

The gliomas of the optic nerve grow so slowly that it is difficult to decide on purely clinical evidence whether or not the tumor has been completely removed and a cure effected. This slow growth has lulled many surgeons into a false sense of security. There are reports of patients who have survived for long periods (up to 20 years, according to Hudson) even after obviously incomplete removal of the tumor.[6] Yet other cases are found in which the tumor was apparently completely removed by an orbital approach but the patient died from intracranial extension of the tumor many years later.[7] One fifth of Byers' and Hudson's patients had intracranial involvement. The rate of intracranial extension was probably even higher, since few patients are followed for a long period, few come to autopsy and the intracranial involvement is not detected until the optic foramen is enlarged, the visual defect extends to the opposite eye or signs of increased intracranial pressure occur.[8] However, there seems to be a reluctance to abandon the excision of optic nerve tumors by the anterior approach, even though its proponents admit that complete removal of the tumor may not be possible.

Since the advent and refinement of neurosurgical technics, optic nerve tumors have been attacked by an approach through the frontal bone. A flap of frontal bone is reflected, and the dura mater is elevated from the anterior fossa of the skull. The orbit and the optic foramen may then be unroofed and the entire extent of the optic nerve and the other intraorbital structures visualized. At least 21 such operations for optic nerve tumor have been reported in the past 30 years.[9]

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6. (*a*) Byers, W. G. M.: Primary Intradural Tumors of the Optic Nerve, Stud. Roy. Victoria Hosp. **1**:3-82, 1901. (*b*) Hudson.[4] (*c*) Hudson and others.[5] (*d*) Lundberg, A.: Ueber die primären Tumoren des Sehnerven und der Sehnervenkreuzung, Inaugural Dissertation, Karolinska Institutet, Stockholm, Nordiska Bokhandeln, 1935.

7. Byers.[6a] Hudson.[4]

8. Dandy, W. E.: (*a*) Prechiasmal Intracranial Tumors of the Optic Nerves, Am. J. Ophth. **5**:169-188, 1922; (*b*) Results Following Transcranial Operative Attack on Orbital Tumors, Arch. Ophth. **25**:191-216 (Feb.) 1941. (*c*) Gluck, B.: Glioma of the Optic Nerve, Brit. J. Ophth. **16**:406-415, 1932.

9. Dandy,[8a, b] Davis,[1] Gomes, J. P.: Tumors of the Optic Nerve, Am. J. Ophth. **24**:1144-1169, 1941. Grinker, R. R.: Tumors of the Optic Nerve, Arch. Ophth. **4**:497-508 (Oct.) 1930. Hudson and others.[5] Katzin, H. M.: Glioma of the Optic Nerve, J. Mt. Sinai Hosp. **11**:332-335, 1945. Levitt, J. M.: Tumor of the Optic Chiasm and Optic Nerves: Report of a Case, Arch. Ophth. **18**:91-94 (July) 1937. Lundberg.[6d] Mannheimer, M.: Glioma of the Optic Nerve, Am. J. Ophth. **29**:323-328, 1946. Martin and Cushing.[3] Mehnev, G. H.: Primary Tumor of Optic Nerve: Report of 3 Cases, Arch. Ophth. **16**:95-102 (July) 1936. Rand, C. W.; Irvine, R., and Reeves, D. L.: Primary Glioma of the Optic Nerve; Report of Case, ibid. **21**:799-816 (May) 1939. Wilson, J. M., and Farmer, W. D.: Glioma of the Optic Nerve: Critical Review; Report of Two Cases, with Autopsy Observations in One, ibid. **23**:605-618 (March) 1940.

Opinion is divided with regard to whether all optic nerve tumors should be exposed by a transfrontal approach. Some authors state that if there is no evidence of intracranial extension, such as enlargement of the optic foramen, and the tumor appears to be entirely intraorbital, an approach through the orbit should be made.[10] These authors reserve the frontal operation for patients with obvious involvement of the intracranial portion of the optic nerve. However, the intracranial extension may be present without enlargement of the optic foramen or other signs. By the time obvious involvement of the optic chiasm or invasion of the cerebrum has occurred, the tumor has already become inoperable.

Since the extent of the tumor may not be apparent prior to operation, it seems more logical to use the transfrontal approach in all cases of optic nerve tumor. Furthermore, it is usually desirable to resect the intracranial as well as the intraorbital portion of the optic nerve in order to assure as complete a removal of the tumor as possible and thus to insure the best possible results. Thus, all eventualities may be dealt with only by the transfrontal approach.

If a coronal scalp incision is made with downward reflection of the frontal portion of the scalp, no visible scar is left. Enucleation of the globe can be done as a second stage operation. If 10 to 14 days are allowed to elapse between operations, sufficient healing will have taken place after the transfrontal operation so that the enucleation can be done without fear of meningitis.

There is universal agreement that the tumors involving the optic chiasm are not amenable to surgical measures and are best treated with roentgen irradiation.

The following case illustrates the advantageous utilization of the transfrontal approach to intraorbital tumors.

REPORT OF CASE

History.—J. T., a white boy aged 10 years, entered the Chicago Memorial Hospital on June 27, 1948. In November 1947 his parents first noticed that the left eye was more prominent than the right. This protrusion of the left eye was gradually progressive. Decreased visual acuity of the left eye was also noted. There were no other complaints.

Examination.—On April 2, 1948 examination was made by Dr. H. D. Wright, Columbus, Ohio, who made the following report: "External examination at that time revealed visual acuity of 20/20 in the right eye and 20/40 — 2 in the left eye. There was moderate exophthalmos of the left eye, and the scleral veins of the left eye were particularly prominent. In the Worth four dot test he suppressed the left eye at both distance and near. It was also noted that he suppressed the left eye in all the six cardinal directions of gaze. Examination of the muscles at that time revealed 2 p. d. of esophoria and 0.5 D. of left hyperphoria at near. At distance he showed 2 p. d. of exophoria with no vertical imbalance. At that time cycloplegic

10. Braendstrup, P.: Primary Tumours of the Optic Nerve, Acta ophth. **22**: 72-94, 1944. Dandy,[5a] Gluck,[5c]

refraction revealed that vision in the left eye could not be improved above 20/40. . . . Ophthalmoscopic examination revealed no abnormalities in the fundus of either eye. The basal metabolic rate was — 17 per cent (Sanborn)."

On May 28 the patient was examined by one of us (F. M. W.). Vision was 20/25, correctible to 20/20, in the right eye and 20/100, correctible to 20/40, in the left eye. Measurement showed the right eye to be 11.5 mm. from the orbital rim and the left eye 15 mm. There seemed to be something solid behind the left eye, as the globe was not easily compressible into the orbit. The visual fields were roughly within normal limits, although the left showed about 10 degrees of depression throughout. There was questionable limitation of motility of the left eye laterally, but no diplopia could be elicited. The veins of the left fundus were slightly engorged, but there was no choking of the optic disk.

When the patient was admitted to the hospital, on June 27, examination revealed no essential change in the condition of the left eye as compared with that of May 28. It was noted, however, that the left corneal reflex was weaker than the right. There was no abnormality except for that in the left eye. There were no stigmas of neurofibromatosis. The blood pressure was 100/65. The pulse rate was 80. The thyroid gland was not enlarged, and there was no evidence of disturbance of function of any other endocrine gland. Urinalysis and blood counts gave normal results. Roentgenographic examination of the skull and orbits revealed no abnormality. The optic foramens were normal in size and shape.

Operations.—On June 28, with the use of ether anesthesia, a coronal scalp incision was made. The scalp was reflected downward and forward off the frontal bone. A small left frontal osteoplastic flap was reflected separately. A cannula was inserted through the left frontal lobe into the left lateral ventricle. The purpose of this maneuver was to decompress the left frontal lobe and facilitate its retraction for purposes of exposure. However, only a few drops of ventricular fluid were obtained. Therefore a lumbar puncture was done, and the needle was left in place throughout the operation, draining about 80 cc. of spinal fluid. This reduced the pressure in the left frontal lobe, which was then elevated from the roof of the orbit extradurally. The orbit was unroofed by a trephine opening and enlarged with rongeurs, and the orbital fissure and optic foramen were also unroofed. The capsule of the orbit was incised, and the levator palpebrae superioris and rectus superioris muscles were retracted. This disclosed a large tumor of the optic nerve, extending from the posterior part of the globe backward to the optic foramen. The optic nerve within the optic foramen and the entire intracranial portion of the optic nerve appeared normal. The optic nerve was severed about 6 mm. behind the globe. A portion of the tumor and its capsule was excised with a pituitary rongeur and curet. Extirpation of the tumor could not be completed at this operation because of a further rise in intracranial pressure.

Recovery from the first operation was uneventful. Two weeks later, on July 12, the frontal flap was reopened. The left optic nerve was severed just in front of the chiasm and reflected forward to the annulus of Zinn. The tumor was then separated by sharp dissection from its attachment to the annulus and extraocular muscles. This permitted the entire tumor and the optic nerve proximal to the tumor to be lifted free in one piece. The appearance of the tumor at operation and the extent of the resection are depicted in figure 1. The bone flap was replaced, and the scalp was closed in two layers with interrupted silk sutures.

The patient made a good recovery from the second operation. A full visual field in the right eye indicated that the optic chiasm had not been damaged. He was out of bed on the fifth postoperative day and was discharged on the tenth postoperative day.

Because of the proximity of this optic nerve tumor to the globe, it was felt that enucleation would offer the best assurance of complete extirpation of the neoplasm. On August 3 the left eye was enucleated. A 6 mm. piece of optic nerve was attached to the posterior surface of the eyeball.

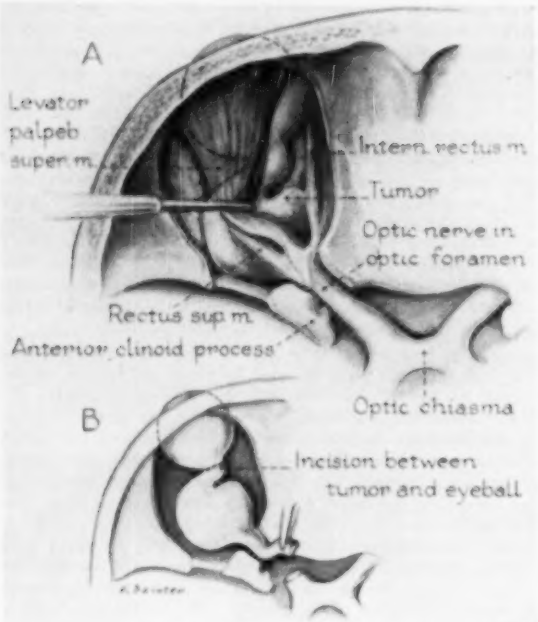

Fig. 1.—*A*, appearance of the glioma of the optic nerve at operation, after unroofing of the orbit and optic foramen. *B*, extent of resection of optic nerve and tumor.

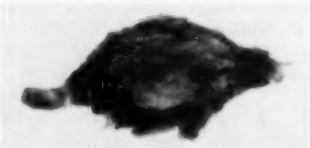

Fig. 2.—Gross appearance of the tumor and resected portion of the optic nerve. The intracanalicular and intracranial portions of the optic nerve lie to the left.

Pathologic Study.—The gross appearance of the tumor and resected portion of the optic nerve is illustrated in figure 2. Sections of the tumor were stained with hematoxylin and eosin and by Van Gieson's method and impregnated by Bodian's strong silver protein (protargol®) method, Perdrau's method for reticulin and

Hortega's method, fourth variant. The tumor tissue was composed of elongated, spindle-shaped cells of rather uniform appearance. The cells had a distinct tendency toward a parallel, streaming arrangement. The nuclei were ovoid and contained a moderate amount of chromatin material. The tumor cells seen in a section stained by the method of Hortega (fourth variant) had an appearance typical of unipolar spongioblasts (fig. 3). There was virtually no connective tissue within the tumor itself except that in the blood vessel walls, which were somewhat hypertrophied. There was pronounced thickening, with increase of connective tissue elements, of the meningeal coverings of the tumor, and this thickening extended

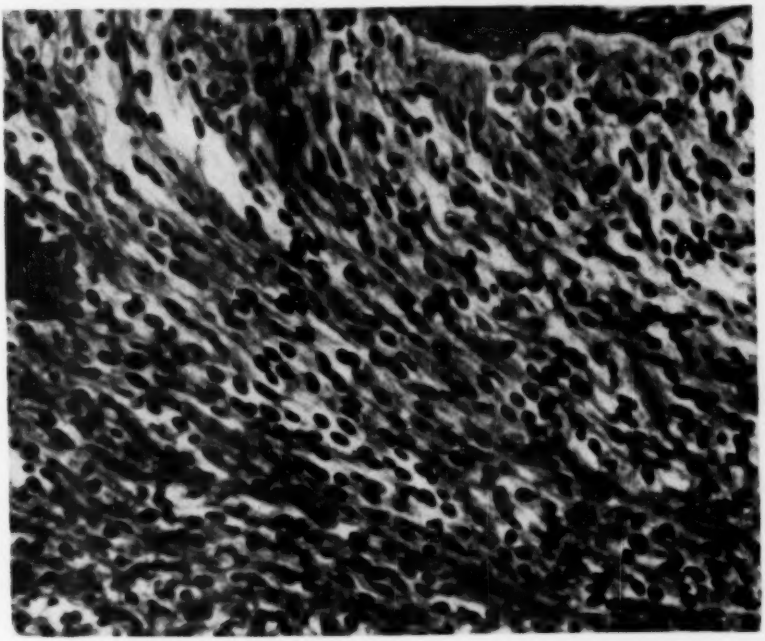

Fig. 3.—Microscopic section of the glioma stained by method of Hortega (fourth variant); × 325.

around the portion of the optic nerve not invaded by tumor. The portion of the optic nerve proximal to the grossly visible tumor was observed to be invaded for a short distance by microscopic amounts of tumor tissue. Sections of the enucleated eyeball showed no invasion of the papilla by neoplasm. The pathologic diagnosis in this case was glioma (spongioblastoma unipolare) of the optic nerve.

Postoperative Course.—The patient's postoperative recovery was excellent. He has continued to enjoy good health, with no visual disturbance in the right eye. When examined 13 months after operation, on Aug. 25, 1949, the visual acuity in the right eye was 20/20, and the visual field was full in that eye. There has been no evidence of increased intracranial pressure.

Comment.—We believe that this patient has been given the best possible chance for a cure. By means of the frontal flap and unroofing of the orbit, it was possible to excise all of the tumor and a considerable portion of the optic nerve proximal to the tumor. Microscopic examination showed that the glioma had not invaded to the posterior limit of excision of the optic nerve. Had an approach been made anteriorly through the orbit, such a wide excision of the tumor and nerve could not have been made, and there is more than a little reason to believe that some tumor would have been left in that portion of the optic nerve which could not have been removed. The outlook with these tumors is poor indeed if the tumor is not completely removed. However, with total extirpation of the neoplasm the results should be excellent, apart from the loss of the affected eye. These patients, often young children, should be given every chance for recovery and cure.

Of course, all intraorbital tumors are not gliomas of the optic nerve. There may be aneurysms,[11] meningeal tumors, xanthomas, lymphomas, primary sarcomas, metastatic carcinomas, dermoids and osteomas. Some of these tumors are incurable by any means, but all are most adequately exposed and most readily dealt with by a transfrontal approach.

Obviously, one is confronted here with a therapeutic problem which transcends the borders of two specialties. It is best handled by cooperation of the ophthalmic and the neurologic surgeon. The neurologic surgeon always welcomes the counsel of the ophthalmologist at the time of his exploration of the orbit, whereas the removal of the bulb, should it be necessary, is best executed at a secondary operation by the ophthalmic surgeon. A similar procedure has been recommended by Ray and McLean [12] in the treatment of unilateral glioma of the retina. They suggested that the intracranial intracanalicular and intraorbital portions of the optic nerve be removed from the bulb to the optic chiasm by the neurologic surgeon and that the eyeball be subsequently removed by the ophthalmic surgeon. We have found this a very satisfactory method of handling these highly malignant tumors. One infant operated on in this fashion at the age of 7 months is still alive and perfectly well, with good function in the remaining eye, now three years and two months later.

25 East Washington Street, Chicago 2 (Dr. Bucy).

899 Madison Avenue, Memphis, Tenn. (Dr. Russell).

826 East Sixty-First Street, Chicago 37 (Dr. Whitsell).

11. Heimburger, Robert F.; Oberhill, H. R.; McGarry, H. L., and Bucy, P. C.: Intraorbital Aneurysm: Case of Aneurysm of the Lacrimal Artery, Arch. Ophth. **42**:1-13 (July) 1949.

12. Ray, B. S., and McLean, J. M.: Combined Intracranial and Orbital Operation for Retinoblastoma, Arch. Ophth. **30**:437-445 (Oct.) 1943.

VERTICAL HETEROTOPIA OF THE MACULA

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HETEROTOPIA of the macula is an extremely rare finding, and a survey of the literature reveals that there are 6 reported cases to the present time from all causes. In addition, there are 3 pathologic demonstrations of this condition in fetal eyes.

The earliest case report is that of Krüger,[1] who described a congenital anomaly of the posterior pole in which both the disk and the macula were displaced laterally so that the nerve head lay in the pupillary axis and the macula was assumed to be far temporal. Triebenstein,[2] in 1919, reviewed the German literature and described 4 previously reported cases, adding 2 of his own. In the 4 former cases, both disk and macula were displaced concomitantly down, up or up and out. These abnormalities were found in conjunction with foci of chorioretinitis, fibrous traction bands and/or colobomas of the choroid and optic nerve.[3] Triebenstein [2] described in the same family 2 cases of multiple anomalies of the posterior pole of the eye resulting in heterotopia of the macula. In both his cases chorioretinitic lesions occurred in the fundus, and in the first "a white, cloudlike opacity extended from the temporal papillary edge like a comet's tail laterally for 1 disk diameter and then lost itself in the retina. A mirror image was present in

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1. Krüger, A.: Angeborene Anomalie der topographischen Verhältnisse am hintern Augenpole: Die Papillen liegen in der Pupillarachse, Ztschr. f. Augenh. **30**:21, 1913.

2. Triebenstein, O.: Ueber Heterotopie des Sehnerven und der Fovea centralis, Klin. Monatsbl. f. Augenh. **62**:442, 1919.

3. Bernhard, A.: Ein Fall von abnormer Lage der Makula lutea und partiellen Colobom der Chorioidea, Arch. f. Augenh. **37**:51, 1898. Adam, M.: Demonstration, in Transactions of Berlin Ophthalmological Society, Centralbl. f. Prak. Augenh. **36**:267, 1912. Lange, O.: Eine Insertionsanomalie des Nervus opticus, Arch. f. Ophth. **51**:342, 1900. Pflüger, E.: Mikrocephalie und Mikrophthalmie, Arch. f. Augenh. **14**:1, 1885.

the fellow eye." In the second case an associated vascular anomaly was present in which all the vessels originated from the nasal edge of the disk and ran in narrow bundles temporally.

Von Beselin [4] reported a case similar to that of Triebenstein. The case of Bielschowsky [5] resembled in certain respects the one to be reported here. His patient presented a marked exotropia and hypertropia simulating a vertical muscle imbalance and, in fact, had been operated on for this condition ten years previously. On the screen test, the left eye deviated down and out in order to fixate an object previously fixed by the right eye, and the right eye assumed an up and out position during fixation. The fundus in this case showed old healed foci of chorioretinitis suggestive of hereditary syphilis.

Stein [6] described a case of heterotopia of the macula with cicatrix of the retina due to ignipuncture for retinal detachment. Friedman [7] reported a case of an unusual macular lesion which probably resulted from birth trauma. Traction bands were seen running to the macula from an area inferior and nasal to it. This caused a pronounced displacement of the macula, as demonstrated by gross displacement of a dense central scotoma representing the fixation area.

REPORT OF A CASE

A white man aged 22 came to the University Hospital of New York University-Bellevue Medical Center to have his glasses checked. On taking the visual acuity, it was noted that the right eye assumed a position of slight abduction and depression on fixation and the left eye assumed a position of considerable elevation and abduction on fixation. On being questioned, the patient stated that he was aware of this condition but was not disturbed by it (fig. 1).

Vision in the right eye was 20/100, improved to 20/30-2 with a correction of $+2.00 \bigcirc -3.00$, axis 90, and 20/30 — 2 in the left eye, improved to 20/20 — 2 with a correction of — 2.00, axis 90.

Ophthalmoscopic examination showed that the macula in the right eye was slightly temporal and inferior to its normal position. The fundus was otherwise not remarkable. The left eye revealed displacement of the macula approximately 1 disk diameter farther temporally and a similar distance above the midline. Thickened branches of the inferior temporal artery and vein struck out obliquely toward the fovea. A moderate-sized artery coursed from the temporal portion of the disk directly toward the heterotopic macula. No inflammatory lesions were seen in either eye under full dilation (fig. 2 *A* and *B*).

4. von Beselin, E.: Scheinbares Höhenschiebe infolge von Narb Verziehung der Fovea, Klin. Monatsbl. f. Augenh. **73**:691, 1924.

5. Bielschowsky, A.: Ein ungewöhnlicher Fall von vertikaler Heterotopie der Makulae, Klin. Monatsbl. f. Augenh. **84**:755, 1930.

6. Stein, R.: Heterotopie der Makula infolge von Zikatrix während Ignipunctur der Netzhaut, Klin. Monatsbl. f. Augenh. **86**:188, 1931.

7. Friedman, B.: An Unusual Disciform Retinal Lesion with Heterotopia Maculae, Arch. Ophth. **28**:444 (Sept.) 1942.

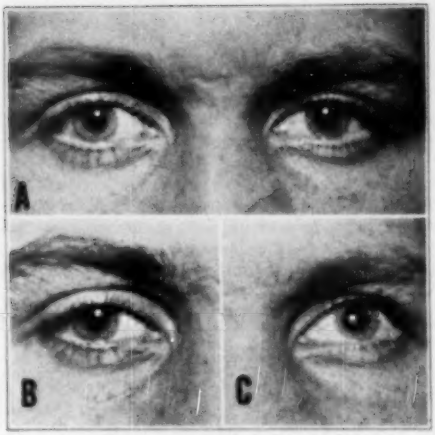

Fig. 1.—*A*, normal appearance at rest, with right eye fixing; *B*, right eye fixing; *C*, left eye fixing. The patient was instructed to fix the camera lens. The light source was held 7 inches (17.5 cm.) above the center of the lens.

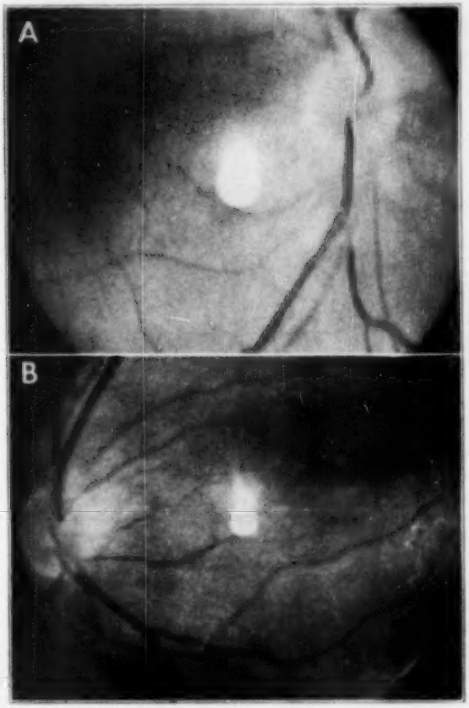

Fig. 2.—*A*, fundus of the right eye, showing macula down and out from its normal position; *B*, fundus of the left eye, showing (1) macula up and out from its normal position; (2) large branches of the inferior temporal vein and artery striking toward the macula; (3) a direct macular branch artery from the temporal margin of the disk.

In order that changes in fixation should be neutralized during the screen and cover tests, prisms were introduced before the left eye. No further motion was noted in the primary position with prisms base out 10△ and base up 20△. In the cover test it was noted that the right eye followed the left when the left traveled up and out to fix. A similar condition obtained with fixation of the right eye. At rest, the patient preferred to fix with the right eye and was conscious of change in position when the left eye fixed. The two eyes moved in parallel in all fields—pseudoversional movements, since the true visual axes were horizontally and verti-

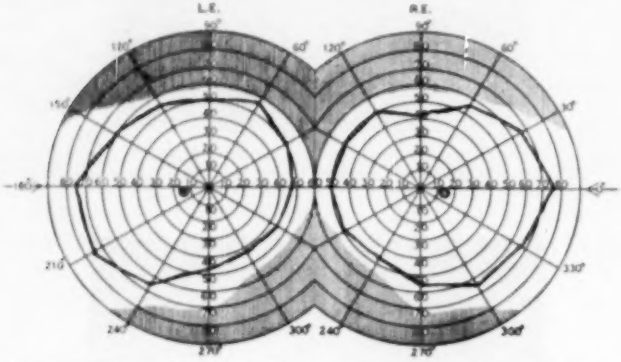

Fig. 3.—Peripheral fields for 3/330 white taken with artificial illumination.

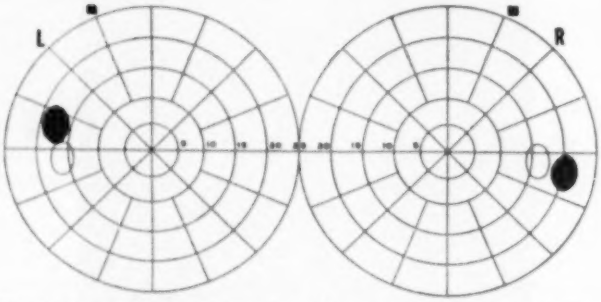

Fig. 4.—Central fields: (1) location and size of the blindspot for 10/1000 white. For 2/1000 white the field extended beyond the chartable area (30 degrees) in both eyes and is recorded as normal. There were no central scotomas.

cally divergent. Examination on the major amblyoscope revealed complete suppression alternately as the angle of fixational difference was approached.

Examination showed normal peripheral fields (fig. 3). Studies on the tangent screen revealed the blindspot of the right eye to be displaced temporarily approximately 2 to 3 degrees and to lie just beneath the horizontal meridian. The blindspot of the left eye was seen to be displaced laterally approximately 5 degrees and to be completely above the midline (fig. 4).

SUMMARY

In all previously reported cases of heterotopia of the macula, whether believed to be on a developmental basis [8] or due to congenital noxious influences, such as hereditary syphilis, lesions of the fundus of chorioretinitis or pigment changes similar to those seen with retinitis pigmentosa have been present. In the majority of instances traction bands could be demonstrated. A case has been noted in which heterotopia maculae followed operation for retinal detachment with ignipuncture, and in another it was due to macular hemorrhage during delivery.

In the case presented the displacement can best be explained as due to abnormal differences in the rates of growth and maturation of the portions of the retina involved.

511 East 20 Street.

303 East 20 Street.

Dr. Harold Whaley Brown gave assistance in the preparation of this report.

8. Mann, I.: Developmental Anomalies of the Eye, London, Cambridge University Press, 1937, p. 157.

CILIUM IN THE ANTERIOR CHAMBER

Report of a Case

JAMES W. SMITH, M.D.
NEW YORK

THE FEAR of infection following penetrating wounds has been lessened considerably since the introduction of antibiotic and chemotherapeutic agents. Ten years ago failure to excise an iris prolapse would have been frowned on as malpractice. The deforming pear-shaped pupil that resulted was deemed a small premium to pay against intraocular infection.

The good cosmetic result achieved in my patient without excision indicates that bad practice in 1940 may be considered good practice in 1950.

Search of the literature reveals that questionable practice still exists regarding perforating injuries which lodge cilia in the anterior chamber. Despite the complications that follow such accidents, many ophthalmologists do not remove the lashes. We have not advanced far since 1924, when a colleague closed his published report on a cilium in the anterior chamber with the statement, "Nothing, of course, was done with it."[1]

HISTORY OF CASE

J. D., a white man aged 23, had worn myopia-correcting lenses for thirteen years, which improved vision to 20/15 in each eye. On Oct. 1, 1949, as he was chopping a long, thin piece of wood with a cleaver, one half of the wood shattered his right eyeglass. When the eye was examined at my office two hours later, the pupil appeared pear shaped (7 by 3 mm.), and the iris was prolapsed through a ragged, 3 mm. laceration of the corneal limbus at 7 o'clock. The exposed portion of the iris measured 2 mm. horizontally and 3 mm. anteroposteriorly. An eyelash was present in the empty anterior chamber. Inferiorly it appeared free in the pupil, but superonasally it was embedded in the iris stroma peripherally at 3 o'clock (figure, *A*). Corrected vision was 20/20.

The conjunctival fornices and anterior chamber were carefully examined for the presence of glass particles. After extensive irrigation of the fornices with isotonic sodium chloride solution the iris prolapse was bathed for ten minutes in a 30 per

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Presented before the New York Academy of Medicine, Section of Ophthalmology, April 17, 1950.

From the Department of Ophthalmology, of the Post-Graduate Medical School and the University Hospital (New York University–Bellevue Medical Center).

1. Hughes, R.: A Cilium Through the Iris Without Symptoms, Am. J. Ophth. **7**:702, 1924.

cent solution of sodium sulfacetimide. Pilocarpine hydrochloride solution, 4 per cent, was instilled to draw the iris back to its normal position. Sulfathiazole ointment, in 5 per cent concentration, was introduced prior to the application of a sterile eye pad and monocular pressure bandage. The patient was admitted to the University Hospital for removal of the cilium and probable excision of the iris prolapse.

On removal of the dressing prior to operation, the pupil was observed to have contracted to 2 mm., and the iris diaphragm was intact except for an adhesion to the anterior lip of the corneal wound.

The anterior chamber was entered with a narrow spatula, but the wound edges were so jagged that an attempt to remove the eyelash with forceps was unsuccessful. It was deemed inadvisable to enlarge the wound, with the possibility of inducing a secondary iris prolapse. The anterior chamber was irrigated with penicillin solution (10,000 units per cubic centimeter); 2 per cent atropine solution was instilled, and a sterile dressing was applied. Penicillin, 300,000 units, and tetanus toxoid U. S. P., 1,500 units, were injected intramuscularly. When the eye was dressed twenty-four hours later, the anterior chamber was found to be fully restored.

Two days after injury biomicroscopic examination revealed that the cilium base was lodged in the iris root at 3 o'clock while the tip was incarcerated in iris stroma midway between the sphincter and the limbus in the 6 o'clock meridian (figure, *B*).

A B C

A, cilium in anterior chamber. The pupil measured 7 by 3 mm.; the iris prolapse was 2 mm. wide and 3 mm. in anteroposterior diameter. *B*, pupil contracted to 2 mm. by instillation of 4 per cent pilocarpine hydrochloride solution. The iris is restored. The site of the keratome section for removal of the cilium is shown. *C*, five weeks after removal of the cilium. The periphery of the iris was adherent to the wound of the corneal perforation without deforming the pupil.

A keratome incision was made in the limbus at 2 o'clock. A narrow forceps was used to enter the anterior chamber, but it engaged iris tissue before the eyelash could be grasped. The keratome section was enlarged to the 2:45 o'clock meridian, and, although the chamber was restored several times with isotonic sodium chloride solution, removal by various types of forceps was thwarted by bulging of the iris. The eyelash was finally engaged with an angulated iris spatula and teased out of the anterior chamber. A small iris prolapse was replaced. Penicillin solution was used to refill the empty anterior chamber. The patient was discharged from the hospital three days after operation.

On examination at the office, papilledema of 3 D. was noted in the right eye, and vision was reduced to 20/30 in that eye. A small vitreous opacity was seen, but roentgenographic examination did not reveal any radiopaque foreign body in the eye or the orbit. Sudden reduction of intraocular pressure following perforation was thought to be the cause of the papilledema. On November 5 the temporal nerve edges were clearly defined and vision had improved to 20/20 +. One week later (six weeks after the accident) the optic nerve appeared normal and corrected vision was 20/15 +. An iris tab inferiorly was adherent to the corneal wound, but the circularity of the pupil was not impaired (figure, *C*).

FREQUENCY

In a recent paper Sitchevska and Payne [2] stated that their 2 cases were the only ones recorded at the New York Eye and Ear Infirmary, out of a total of 374,721 patients with ophthalmic disorders examined between 1932 and 1947. I have regularly attended meetings of this section for the past thirty years but cannot recall a previous presentation on this subject. In a review of the literature made by Sharpe [3] in 1925 he cited only 75 cases in the preceding hundred years. Against these claims of infrequency is Müller's [4] report of 5 cases in Fuchs's Vienna clinic observed among 30,000 patients over a two year period. From 1923 to 1925 five authors [5] published case reports in the *American Journal of Ophthalmology*. No American reports are listed in the *Quarterly Cumulative Index Medicus* since 1942. One case was cited from Argentina [6] in 1942 and another from Brazil [7] in 1943.

A limited investigation made by me in the past few weeks revealed that cilia in the anterior chamber is a rather common finding. Dr. A. Russell Sherman, of Newark, N. J., has had 2 cases within the past five years; Dr. Alson E. Braley, 2 cases in nine years, and Dr. Arthur M. Yudkin, of New Haven, 6 cases in sixteen years. These contributions are particularly noteworthy because the cilia were not removed and the eyes have been free from irritation or attacks of inflammation. Dr. Sherman examined a third patient in consultation, but the eyelash was removed despite his objection. Dr. Donald M. Shafer recently excised an iris prolapse following a severe perforating injury. One cilium was caught in the corneal wound. A second one was removed when a traumatic cataract was extracted. Of the 14 cases collected, in only 3 did the ophthalmologist choose to remove the lashes.

Dr. R. Townley Paton informs me that the records of the Manhattan Eye, Ear and Throat Hospital since 1928 did not reveal a single case. Dr. Arthur G. DeVoe could not furnish data from the Institute

2. Sitchevska, O., and Payne, B.: Cilia in the Anterior Chamber, Am. J. Ophth. **32**:982, 1949.

3. Sharpe, O.: Cilia in the Anterior Chamber, Am. J. Ophth. **8**:301, 1925.

4. Müller, L.: Ueber Zilien in der Vorderkammer und spontane Ausstossung derselben, Wien. klin. Wchnschr. **7**:231, 1894.

5. (*a*) Hughes.[3] (*b*) Gradle, H.: A Cilium in the Anterior Chamber for 19 Years, Am. J. Ophth. **6**:764, 1923. (*c*) Sharpe.[3] (*d*) Franklin, W., and Cordes, F.: Three Cilia in the Anterior Chamber Following Trauma, Am. J. Ophth. **8**:306, 1925. (*e*) Roth, I., and Geiger, C.: Posterior Chamber Cysts of the Iris, ibid. **8**:870, 1925.

6. Damel, C. S., and Durando, S. A.: Quistes traumaticos del iris y pestañas en camara anterior, Arch. oftal. Buenos Aires **17**:614-625, 1942.

7. Belfort Mattos, W.: Um cilio vinte anos na camara anterior, Arq. brasil de oftal. **6**:38, 1943.

of Ophthalmology without undertaking an extensive review of all patients with intraocular foreign bodies. In Davidson's [8] series from the New York State Department of Labor, 80 per cent of foreign bodies perforated the cornea. Statistics reveal that penetrating wounds constitute 5 per cent of all ocular injuries and that intraocular foreign bodies occur in 1 per cent of such injuries. In view of this high incidence of perforating wounds, the only explanation I can offer for the striking lack of cases in three ophthalmologic hospitals is that no separate record room file is maintained for the associated intraocular foreign body finding of cilia in the anterior chamber.

COMMENT

Conflicting opinions prevail regarding the proper management of cases with one or more eyelashes in the anterior chamber. I have always maintained that all intraocular foreign bodies must be removed as soon as feasible. Medicolegally an ophthalmologist would be remiss if he knowingly neglected to do so. However, many cases have been reported in which cilia have remained quiescent for years. Ophthalmologists having this fortunate experience firmly believe that it is best to leave "well enough alone." It should be borne in mind that removal poses some difficulty. Besides the iris prolapse referred to previously the lens may be injured, producing a cataract.

Würdemann [9] clearly stated the reasons for removal.

> Cilia in the anterior chamber following accident or operation are rare but I have seen a dozen cases, in which cysts of the iris formed. Cilia which enter the eye by traumatism are generally tolerated for years without causing the least symptoms. They may, however, give rise to infection, or more or less early to irritation, ciliary injection, photophobia, lacrimation, pain, or to the development of epidermoidal tumors of the iris, cysts, with subsequent glaucoma, blindness or loss of the eye. Therefore, their early removal is indicated, although even then tumors may develop from simultaneously introduced epidermoid particles.

Rothmund,[10] in 1872, established the theory of the mechanical transference of epithelial elements from the surface in the production of the so-called pearl tumors, or epidermoid cysts. He collected 36 cases of traumatic implantation cysts, of which 28 followed perforating wounds, 2 followed cataract operations and 3 were due to inclusion of an eyelash.

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8. Davidson, M.: Lens Lesions in Eye Perforations, Am. J. Ophth. **23**:1358, 1940.

9. Würdemann, H. V.: Injuries of the Eye, ed. 2, St. Louis, C. V. Mosby Company, 1932, p. 499.

10. Rothmund, A.: Zur Pathogenese der Iriscysten, Klin. Monatsbl. f. Augenh. **9**:397, 1871; Ueber Cysten der Regenbogenhaut, ibid. **10**:189, 1872.

The difficulty of later differentiating a cyst from malignant tumor must be considered. According to Duke-Elder,[11] the "list of cysts in the literature which have been excised as tumors by competent observers is significant." One of his American references [12] concerns implantation cysts after lodging of cilia in the anterior chamber. Enucleation followed a clinical diagnosis of melanosarcoma of the iris.

Two cases of sympathetic inflammation from cilia impacted in the anterior chamber have been reported,[13] 1 by Cuvier and another by von Graefe.

The number of cilia that may be introduced usually varies from one to six.[10] Vieweger,[12] who collected *29* cases from the literature in 1883, cited an extraordinary occurrence of fourteen cilia in one case!

SUMMARY

An uncomplicated iris prolapse was restored with a strong miotic without recourse to surgical measures. Use of antibiotics and chemotherapy prevented infection.

If cilia are not removed from the anterior chamber, the patient is needlessly subjected to the risk of implantation cyst formation, glaucoma and loss of vision.

The small number of cases of cilia in the anterior chamber in the literature is not a true index of frequency. Fourteen cases were collected from the private practice of six ophthalmologists, but three large ophthalmologic hospitals could not readily furnish a single case. The inference is that no separate hospital record room file is maintained for the finding of cilia in the anterior chamber. A review of ocular injuries classified under lacerations of the cornea, iris prolapse, penetrating wounds and intraocular foreign bodies would undoubtedly reveal more cases of cilia in the anterior chamber.

1016 Fifth Avenue (28).

11. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2444.

12. Cited by Würdemann, in Duke-Elder,[11] p. 500.

13. Bulson, A.: Five Cilia in the Anterior Chamber, Am. J. Ophth. **3**:128, 1920.

Clinical Notes

INSTRUMENTS FOR CATARACT SURGERY

D. E. ROLF, M.D.
CLEVELAND

LANCE FOR NEEDLING SECONDARY CATARACTS

IT HAS been my experience, in common with that of other surgeons, that one frequently runs into difficulty when one attempts a needling of a secondary cataract. The cataract seems to give way posteriorly instead of being incised according to standard technics. The principle used in cutting the membrane is the application of force posteriorly or anteriorly by a pushing motion. I have therefore devised a small lance which is barb shaped and has a sharp anterior tip. The inner surface, which is notched, is also razor sharp, and the instrument is used in the following manner:

Fig. 1.—Lance for needling secondary cataracts.

The lance penetrates the cornea to the limbic border and is then rotated vertically to engage the secondary membrane. The small sharp anterior tip perforates this membrane very easily, and the instrument is then pulled forward in an inverted V manner. The membrane is caught in the very sharp notch on the inner surface of the lance and is, therefore, dissected very easily as the lance is pulled forward. After the incision has been completed, the lance is again rotated horizontally on its flat surface and extracted from the anterior chamber.

I have found that this instrument, by catching the membrane in the V-shaped anterior notch, keeps it from being pushed backward into the vitreous. I have also found that it is much easier to dissect the tissue by a "pulling" rather than by a "pushing" motion. The instrument measures 12 mm. in length. It can be obtained from V. Mueller & Company, Chicago.

MODIFIED CORNEAL RING

This modified corneal ring was adapted from the standard Verhoeff ring, which I have used in cataract extractions for some time. However, it differs in several important respects. First of all, it is stirrup shaped, and the lower border is concave to conform to the convexity of the

lower limbic border of the cornea. Second, it has a wider diameter, in order to encompass a larger area of cornea and thus help in exerting a more even and sustained counterpressure on the vitreous and lens. Third, the whole anterior surface is concave, so that a larger area of

Fig. 2.—Modified corneal ring.

lens is "encased," and this helps immeasurably in the extraction of the cataract. I have used this instrument for some time and personally find it quite advantageous over the instruments commonly used for expression. It can be secured from V. Mueller & Company, Chicago.

1017 Republic Building (15).

GONIOTOMY KNIFE AND SURGICAL CONTACT GLASS

OTTO BARKAN, M.D.
SAN FRANCISCO

THE TECHNIC of goniotomy in treatment of congenital glaucoma has recently been published.[1] In the present communication the description and specifications of the instruments are given.

GONIOTOMY KNIFE

The shaft of the goniotomy knife (figs. 1 and 2) is tapering, oval and 25 mm. in length, the longer diameter of the oval being parallel with the cutting edge of the blade. The measurements of the blade and shaft are such that the wound is sealed throughout the operation. To secure the shape of the blade and the degree of taper of the shaft which will, on the one hand, prevent loss of aqueous and, on the other, not offer too much resistance to easy insertion and passage across the chamber, exact specifications, as given on the mechanical drawing to 0.01 mm., must be followed. The degree of taper of the shaft is not so great that it resists insertion as it progresses through the puncture created by the

Fig. 1.—Photograph of knife.

cutting blade. The blade need not be too keen nor the point too sharp, as it is used to strip tissue from the angle and not to incise it. The tip is sharp enough to permit easy puncture of the cornea. Slight resistance offered by the shaft during the stripping is welcome, since it gives the operator a feeling of guidance and of deliberate movement.

SURGICAL CONTACT GLASS

The surgical contact glass is a gonioscopic lens which is cut off on one side to permit insertion of the knife through the cornea near the limbus. The temporal wall of the lens is ground to an angle of 30 degrees from the horizontal, providing considerable overhang of the upper surface to increase the useful visual angle through the lens. It is made of optical crown glass of index 1.523. It must be handled with care, as its edges are easily chipped. Plastic lenses do not give sufficient clarity of vision. Two small depressions are drilled into the upper surface in order to prevent the finger which holds it in position from slipping. Two sizes of contact glass are used, the infant's (fig. 3 *A*) and medium (fig. 3 *B*), depending on the diameter of the cornea

1. Barkan, O.: Technic of Goniotomy for Congenital Glaucoma, Tr. Am. Acad. Ophth. **52**:210 (Jan.-Feb.) 1948.

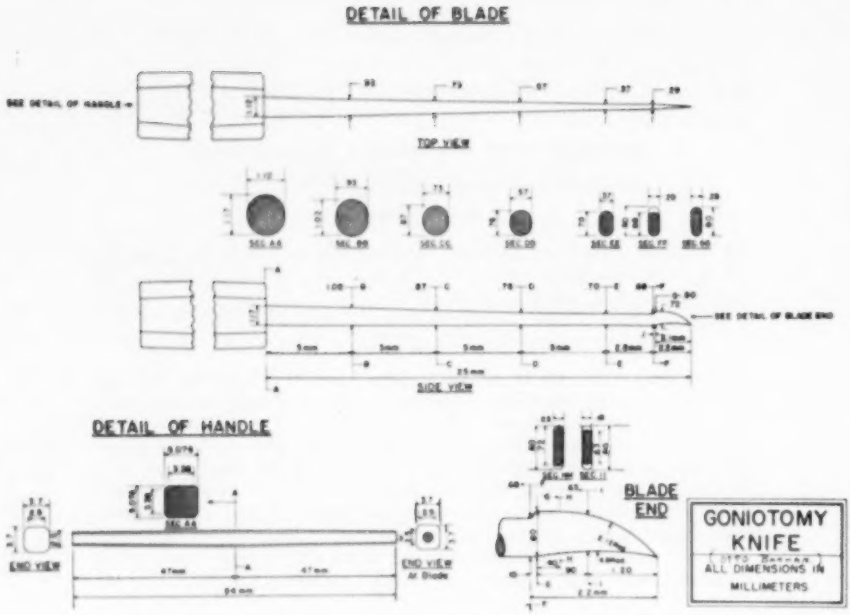

Fig. 2.—Mechanical drawing of knife. All dimensions are in millimeters.

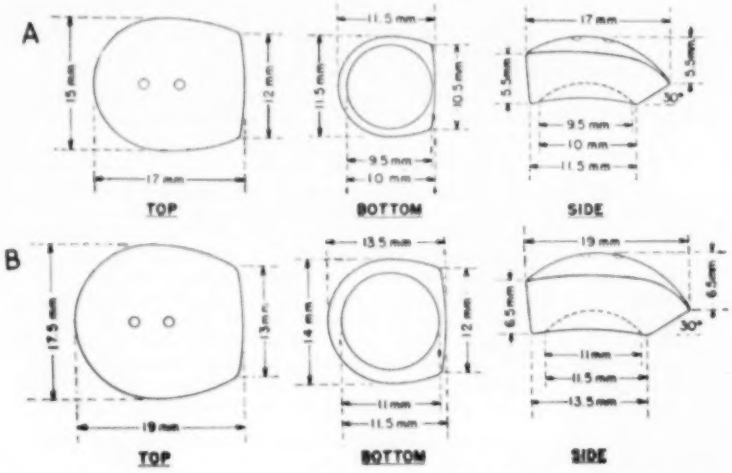

Fig. 3.—Schema of surgical contact glass: *A*, infant's size; *B*, medium size.

and the orbit. It is advantageous to use the medium-sized glass, which has an over-all diameter of 13 mm., because of the greater magnification (× 1.4) and field it affords. But the small size of the orbit in infants under the age of 2 months may not provide enough room between glass and orbital rim to allow for fixation. In this case, the infant's glass, which has an over-all diameter of 11 mm., is used. The measurements of the two glasses are given in the schema.

490 Post Street.

TECHNIC FOR LACRIMAL SYSTEM IRRIGATION

THEODORE N. ZEKMAN, M.D.
AND
MANUEL L. STILLERMAN, M.D.
CHICAGO

THE GENERAL principles in the management of the obstructed lacrimal passage are well delineated. Although differences of opinion do exist regarding specific indications for therapy, competent clinicians agree that the most physiologic and least traumatic approach in each case is desirable. Each case must be carefully evaluated on the basis of such factors as the age of the patient, the duration of obstructive symptoms, the acuteness of the process, the presence or absence of collateral cellulitis, the cause of the obstruction and the previous therapy. An adequate assessment having been made, it ultimately becomes necessary to determine (*1*) whether the stenosis is due to cicatrix or to inflammatory infiltration and edema and (*2*) the degree of the closure.

Most methods for establishing the patency of the lacrimal system consist of irrigation into the nose via the upper or the lower canaliculus. Many times such a regimen fails because the block in the lower part of the system is sufficiently strong to force the injected fluid out of the opposite punctum in retrograde fashion. The logical conclusion, then, is that an insuperable closure exists and that some type of dilating probe should be passed beyond the constricted area into the nasal exit.

We agree with those who feel that passage of an instrument should be circumvented, if possible, because of the danger of added trauma and scarring. Probing can often be avoided by blocking one punctum while fluid is gently, but firmly, injected through the opposite punctum. This creates a pressure head of a magnitude not obtainable in an "open" punctocanalicular system, and one is often able to force fluid and inflammatory products past the stricture. In babies with a persistent congenital membrane at the end of the nasolacrimal duct, sufficient force may be created to rupture the membrane without probing by using this technic. The frequency of such irrigations will be dictated by the findings in the individual patient.

No originality is claimed for the creation of a "closed" punctocanalicular system described in the following section, but since no description of this technic could be found it is presented as a matter of record.

DESCRIPTION

If routine irrigation has failed, the upper and lower lacrimal puncta on the affected side are dilated with the sharp and/or dull punctum dilator (fig. 1). The Heath dilator is pictured, but the Nettleship-Wilder or the Gifford modification with its conical tip are as satisfactory. The

From the Department of Ophthalmology of the University of Illinois College of Medicine.

Fig. 1.—Left, Heath dull and sharp lacrimal punctum dilators; right, Tenner lacrimal cannula.

Fig. 2.—Dilator in upper punctum and irrigating cannula in lower punctum.

upper punctum is exposed either by rolling the lid margin outward or by everting the upper lid while the patient looks down and temporally. The dull punctum dilator is then passed into the upper canaliculus and held firmly so that a watertight seal is created. The assistant then hands the operator a syringe which is filled with the irrigating fluid of choice and is equipped with the Tenner lacrimal cannula (fig. 1, right). The cone-shaped tip forms a tight seal once the tip has passed into the canaliculus, and regurgitation of fluid is prevented. The perforation on the side leaves a smooth tip as the leading point, and passage is atraumatic. The assistant everts the lower punctum by drawing the lower lid down and out while the patient looks temporally and up. The operator inserts the cannula into the proximal part of the lower canaliculus and injects the fluid under steady pressure (fig. 2).

109 North Wabash Avenue (2).

Annual Reviews

THE ORBIT

Review of the Literature

F. BRUCE FRALICK, M.D.
ANN ARBOR, MICH.

A PROMINENT feature of the literature on the orbit during the past year is the large number of articles dealing with orbital tumors and with exophthalmos. It would almost seem that through the years these subjects would have been exhausted, and yet outstanding contributions have been made in these conditions. No attempt will be made to summarize all the articles published, and it is even quite likely that all articles related to the orbit were not available to me.

Benedict,[1] as a result of reviewing 740 orbital tumors, points out that it is not always possible to make a definite diagnosis of a pathologic disorder within the orbit on the basis of the clinical findings alone. Additional findings obtained by a general physical examination and laboratory studies are often needed to make the diagnosis, and even with these diagnostic aids he was often at a loss to make the diagnosis without an orbital biopsy.

A trial of roentgen therapy is indicated before a biopsy specimen is taken, since localized lymphoblastoma may be present in the orbit even before blood studies or lymphadenitis reveals its existence. The presence of adenitis indicates that a gland should be removed for study before the orbit is opened, thus aiding in the diagnosis, as in Orsoni's [2] case.

Diagnostic aids, such as biopsy of material taken with a large hollow needle or trochar, are mentioned only to be condemned, even though Pallarés [3] was aided in arriving at a preoperative diagnosis by such methods. An aneurysm, or encephalocele, although relatively rare, might be encountered. Benedict [1] makes the wise statement that when a biopsy specimen must be taken the surgeon should not attempt it if he is not prepared personally to carry out whatever procedure is indicated or to take care of any complication that might arise as a result of the operation.

1. Benedict, W. L.: Surgical Treatment of Tumors of the Orbit, Am. J. Ophth. **32**:763-773 (June) 1949.

2. Orsoni, J.: Orbital Localization of Malignant Lymphogranuloma, Gior. ital. oftal. **2**:129-136 (March-April) 1949.

3. Pallarés J.: Importance of Microscopic Examination of Puncture Fluid in Diagnosis of Sarcoma of the Orbit: Report of a Case, Arch. Soc. oftal. hispano-am. **9**:60-66 (Jan.) 1949.

To facilitate diagnostic accuracy, Benedict [1] divides the orbit into three surgical zones and three anatomic divisions: Zone 1 extends from the orbital septum to the equator of the globe; zone 2 extends from the equator of the globe to 10 mm. behind the globe, at the point where the central artery and vein of the retina enter the optic nerve, and zone 3 extends from zone 2 to the apex of the orbit. The anatomic divisions are as follows: Division 1 includes tissues peripheral to the subperiosteum. In this division are found the secondary cranial meningiomas as the most frequent neoplasms with the associated roentgenographic changes about the orbit, as listed by Craig and Gogela.[4] Division 2 includes the tissues between the periosteum and the muscle cone, and in this division are found numerous vascular and neoplastic tumors. The 17 primary intraorbital meningiomas reported by Craig and Gogela [4] were either in this division or in division 3. Division 3 includes tissues contained in the muscle cone. The proptosis produced by the lesions in this anatomic division is directly forward. Visual loss from pressure on the optic nerve is more likely. Primary intraorbital meningiomas, as reported by Craig and Gogela,[4] are most frequent; they tend to occur during the middle years of life and are four times as common in women as in men.

The difficulty encountered in the diagnosis of orbital tumors at times makes it imperative that the ophthalmologist have knowledge of all diagnostic aids. An axial stratigraphic study of the orbit, as reported by Pessagno,[5] whereby any desired layer or section of the orbit is visualized and photographed to the exclusion of other layers, may aid in the differential diagnosis of tumors of the orbit. The diagnosis of orbital tumors by angiography, either by the direct or by the open method, is presented by Grino and Billet [6] as a harmless procedure, permitting roentgenologic visualization of orbital as well as intracranial tumors. These authors were able to make accurate localizations by angiographic visualization in three types of orbital tumors presenting similar signs. They feel this method is preferable to, and less dangerous than, less informative methods, such as pneumoencephalography, punch biopsy [2] or intraorbital injection of air. As proof that angiography has already proved its value as an aid in the diagnosis of orbital lesions, Taptas [7] listed angiographic findings in an analysis of cases of pulsating exophthalmos due to arteriovenous communication, and Petit-Dutaillis and

4. Craig, W., and Gogela, L. J.: Intraorbital Meningiomas, Am. J. Ophth. **32**:1663-1680 (Dec.) 1949.

5. Pessagno, A.: Study of the Normal Orbit by Axial Stratigraphy, Ann. ottal. e. clin. ocul. **75**:210-215 (June) 1949.

6. Grino, A., and Billet, E.: Diagnosis of Orbital Tumors by Angiography, Am. J. Ophth. **32**:897-911 (July) 1949.

7. Taptas, J. N.: Etiology and Pathogenesis of Vascular Exophthalmos—Pulsating Exophthalmos, Bull. soc. d'opht. de France, March 1949, pp. 449-455.

associates [8] were able to eliminate a vascular lesion as the cause of pulsating exophthalmos in a case of orbital malformation associated with Recklinghausen's disease (neurofibromatosis).

The measurement of the retrobulbar resistance (orbitonometry) has up to the present time been an indefinite determination, especially in cases of orbital new growths which do not give rise to protrusion of the globe. Cooper [9] has devised an orbitonometer which resembles an exophthalmometer. The eye is more or less pressed into the orbit with various weights, and graphic curves give a clear impression of the degree of displacement of the eye caused by a certain weight. The shape of the curve indicates the degree and course of displacement of the eye. Repeated orbitonometric measurements may show an increasing density of the orbital tissues, giving an impression of the rapidity of growth of the neoplasm.

There is no universal agreement as to the normal values for exophthalmometric readings. Knudtzon [10] took Hertel exophthalmometer readings on 724 normal adults and found the measurements for 99 per cent between 12.1 and 22.3 mm. He observed that the measurements increased slightly with age. Measurements of 20.5 to 21 mm. were considered as highly suspicious, if there was no excessive myopia, and values of 22 mm. or more as pathologic. Fifty-six per cent of the subjects showed a difference of 0.5 to 2.5 mm. between the two eyes, although the difference of more than 1 mm. was rare.

Several reports of vascular lesions of the orbit leading to pulsating exophthalmos were encountered. Of special interest was one by Lisch [11] of a case of familial occurrence of spontaneous pulsating exophthalmos. The father died at the age of 47 of apoplexy following a sudden protrusion of his right eye two years previously. A son had a similar condition in the same eye at the age of 23. The condition was not recognized, since pulsations and murmurs were lacking. A Krönlein operation was followed by severe hemorrhage, necessitating exenteration of the orbit. A sister acquired the disease in the left eye at the age of 45 and in the right eye at the age of 47 and thereafter died of apoplexy. At this time the brother declared he had also had tinnitus, which had disappeared after the exenteration.

8. Petit-Dutaillis, D.; Feld, M., and Taptas, J.: Unilateral Exophthalmos Caused by Orbital Malformations in Recklinghausen's Disease [Neurofibromatosis], Rev. neurol. **81**:203-211 (March) 1949.

9. Cooper, A. C.: Measurement of Retrobulbar Resistance (Orbitonometry) in the Clinic, Nederl. tijdschr. v. geneesk. **93**:3521-3524 (Oct. 8) 1949.

10. Knudtzon, K.: On Exophthalmometry, Acta psychiat. et neurol. **24**:523-537 (Sept.) 1949.

11. Lisch, K.: Familial Incidence of Spontaneous Pulsating Exophthalmos, Ophthalmologica **117**:180-185 (March) 1949.

Heimburger and associates [12] point out that in the literature the term pulsating exophthalmos has become almost synonymous with a diagnosis of fistula between the internal carotid artery and the cavernous sinus. They feel that this trend is erroneous. Likewise, there are six case reports in the literature of intraorbital aneurysm, but few of these cases give satisfactory evidence that the exophthalmos was due to a simple aneurysm limited to the orbit. Heimburger and his colleagues [12] report a case of nonpulsating exophthalmos of the left eye of two months' duration, with distention of the periorbital, conjunctival and retinal vessels, paralysis of ocular movements, blurring of the optic disk, reduced vision, ptosis and a small, sluggish pupil. Transcranial exploration of the orbit allowed removal of an aneurysm of the lacrimal artery. This case shows that true intraorbital aneurysm is rare but that it may be present without pulsation, but with the other signs of venous obstruction, secondary glaucoma, proptosis and visual loss.

With adequate modern chemotherapy and use of antibiotics, fewer patients die of cavernous sinus thrombosis than formerly, and the reports of this condition during the past year record only cures. Miklós [13] advises that in grave cases the treatment begin with cisternal punctures and change to lumbar punctures after the condition has become less grave. The question arises whether with the intrathecal treatment penicillin should be given intracisternally or by lumbar injection. There is no doubt that the puncture of the cistern is much easier for both physician and patient because of its simple technic. It must also be admitted that penicillin which reaches the cisterna cerebellomedullaris is more efficacious than that given by lumbar puncture. It is effective even when there is a spinal block. Miklós' treatment consists of intrathecal administration of 20,000 units of penicillin twice daily as long as the serious symptoms persist, and later of 20,000 units once daily. Intrathecal treatment should not be discontinued before the cell count of the spinal fluid is below 100 per cubic millimeter. In addition, he gives blood transfusions of 100 cc. daily, sulfonamides and 20,000 units of penicillin intramuscularly every three hours.

An excellent cross sectional view of orbital tumors in general is presented by Forrest,[14] who analyzed *222* intraorbital tumors from the Army Medical Museum; 184 were primary tumors, 93 being mesenchymal in origin, 48 from the nervous system, 25 mixed tumors and 18

12. Heimburger, R. F.; Oberhill, H. R.; McGarry, H. L., and Bucy, P. C.: Intraorbital Aneurysm: A Case of Aneurysm of the Lacrimal Artery, Arch. Ophth. **42**:1-13 (July) 1949.

13. Miklós, A.: Cure of Cavernous Sinus Thrombosis, Brit. J. Ophth. **34**:235-241 (April) 1950.

14. Forrest, A. W.: Intraorbital Tumors, Arch. Ophth. **41**:198-232 (Feb.) 1949.

dermoids. The benign mesenchymal growths (19 lipomas, 5 osteomas, 2 fibrolipomas, 2 fibromas, 1 chondroma and 1 rhabdomyoma) occurred in persons of all ages and were situated anteriorly in the orbit, so that they could be removed by the anterior route. The malignant tumors (13 sarcomas, of different types) occurred characteristically in a young age group (under 20 years) and were situated posteriorly in Benedict's orbital zones 2 and 3. One third of these patients having malignant tumors died early, and only one third survived the operation by five years or more. These facts further emphasize the need for early and radical treatment of these tumors. The vascular tumors (24 hemangiomas, 1 angiosarcoma) are rarely malignant. One half of these lesions were situated anteriorly in the orbit, and one half caused exophthalmos. The tumors appear usually in the early years of life. Frequently, because of the difficulty of complete removal, there remains a modicum of tumor, which leads to recurrence. A transcranial approach to the orbit, as advocated by Craig and Gogela [9] and others,[15] gives more adequate exposure and greater ease of complete removal of these tumors.

Growths of the hemopoietic system (22 lymphomas and lymphosarcomas; 2 cases of Hodgkin's disease; 1 plasmocytoma) were initially isolated lesions, and in only two instances was an abnormal blood picture found. The high radiosensitivity of both the benign and the malignant lymphomas give validity to Benedict's [16] dictum that a trial of roentgen therapy be given in those cases in which the preoperative diagnosis cannot be made adequately, even in the face of a negative blood picture. These tumors occurred largely in persons over 40 years of age. Nearly all these patients presented themselves either with a palpable mass in the anterior part of the orbit or with exophthalmos.

Mixed tumors [5] of the lacrimal gland gave as their initial symptom in every instance either a palpable mass or proptosis. Tumors in this anterior location are removed through the anterior route, and the first surgeon to operate has the best chance of effecting a cure. Esente [17] and Fleming [18] feel that these tumors justify a much more guarded prognosis in a high percentage of cases. Incomplete or piecemeal removal usually leads to recurrences after sufficient time.

15. (*a*) Benedict.[1] (*b*) Löhlein, W., and Tönnis, W.: The Surgical Treatment of New Growths of the Optic Nerve Beyond the Optic Foramen, Arch. f. Ophth. **149**:318-354 (Sept.) 1949. (*c*) Naffziger, H.: Exophthalmos and Its Surgical Treatment, Am. J. Ophth. **32**:857-858 (June) 1949.

16. Benedict, W. L.: Diseases of the Orbit, Tr. Am. Acad. Ophth. **54**:26-36 (Sept.-Oct.) 1949.

17. Esente, I.: Contribution to the Study of Cylindromatous Tumors of the Lacrimal Gland, Gior. ital. oftal. **2**:193-213 (March-April) 1949.

18. Fleming, N.: Adeno-Carcinoma (Mixed Tumor) of the Lacrimal Gland, Brit. J. Ophth. **33**:763-769 (Dec.) 1949.

Neural and meningeal tumors (17 neurofibromas, 17 meningiomas, 5 gliomas, 9 neurofibrosarcomas) occurred at all ages. They usually showed slowly progressive exophthalmos with gradual loss of vision. The initial symptoms of this group, as shown by Standal [19] and others,[20] appear usually during the first half of life. Buffat [21] and others [22] feel that the transcranial route of approach best meets any contingencies which may arise in the attack on these tumors, since it would expose an associated intracranial tumor.

All but one of the tumors of developmental origin (17 dermoids, 1 teratoma) were present in the anterior part of the orbit and could be removed by the anterior route. Symptoms did not appear usually until the patient was about 22 years of age.

Of 38 secondary orbital tumors (24 carcinomas, 6 neuroblastomas, 6 malignant melanomas, 1 retinoblastoma and 1 adenoma), most occurred in advancing years except in the case of retinoblastoma and neuroblastoma. These tumors are all highly malignant and show an early mortality. When the tumor has extended to involve the orbit, local removal is then only a temporizing measure.

It is evident from the literature of 1949 that the neurosurgeon has proved to the ophthalmologist the value of the transcranial route of approach for the removal of orbital lesions. Eleven articles [23] mentioned this approach in the care of certain tumor types. The predominant tumors which seemed to indicate the transcranial approach were the vascular lesions, neural and meningeal tumors, cephalocele and meningomyelocele. The cooperation of an ophthalmologist in removal of the tumor from the orbit should be elicited. His knowledge of the anatomy of the orbit would assure the least possible damage to the orbital structures and thus retain the greatest degree of motility of the globe.

Of the rarer lesions of the orbit which give the symptoms of a retro-orbital mass, sarcoidosis has been reported in several instances

19. Standal, B.: Neurinoma of the Orbit, Acta ophth. **28**:49-70, 1950.

20. (*a*) Craig and Gogela.[4] (*b*) Larmande, A. M., and Descuns, P.: Intraorbital Neurinoma Removed by the Temporal Route, Afrique franç. chir., May-July 1949, pp. 129-130.

21. Buffat, J. D.: Neurosurgical Treatment of Tumors of the Optic Nerve, Rev. méd. Suisse rom. **69**:511-522 (Aug.) 1949.

22. Standal.[19] Craig and Gogela.[4] Buffat.[21]

23. Forrest.[14] Sabbadini, D.: Neuro-Fibro-Angioma of the Orbital Infundibulum, Oto-neuro-oftal. **24**:207-216 (March-April) 1949. Petit-Dutaillis and others.[5] Larmande and Descuns.[20b] McFarland, P. E., and Eisenbeiss, J.: Glioma of the Optic Nerve, Am. J. Ophth. **33**:463-466 (March) 1950. Standal.[19] Benedict.[16] Craig and Gogela.[4] Strandberg, B.: Cephalocele of Posterior Part of Orbit: General Survey, with Report of Case, Arch. Ophth. **42**:254-265 (Sept.) 1949. Löhlein and Tönnis.[15b] Buffat.[21]

(two by Benedict,[24] one by Rider and Dodson,[25] one by Bodian and Lasky,[26] one by Knapp and Knoll[27]). Benedict's[24] report is based on a study of over 1,000 cases of orbital tumor seen over a period of 23 years. Orbital complications have not occurred in any of his other cases of sarcoidosis, but intraocular manifestations, such as iritis, choroiditis and uveitis, have frequently been seen. The diagnosis of sarcoidosis is made after operation when animal inoculation, bacterial cultures and pathologic examination of excised tissue fail to disclose any etiologic agent. Orbital parasitic cysts continue to appear in the Latin countries. Junior[28] comments that the complement fixation reaction of the blood is a valuable aid to diagnosis, being positive in 73.2 per cent of his cases.

Trauma to the orbit never ceases to present problems in diagnosis and treatment. King and Walsh,[29] in their excellent article on trauma to the head, present the differential diagnosis of "black" eye and orbital fracture:

1. With fracture of the base the extravasated blood is limited sharply by the palpebral fascia to the orbital margins, and thus it tends to be circular. In "black" eye there is no such limitation. Blood is said to extend along the torn dura and bone to become visible several hours, or even several days, after the injury.

2. With fracture of the base the discoloration of the conjunctiva is purplish from the commencement, whereas with "black" eye it is beefy red. With "black" eye hemorrhage is in the conjunctiva and the mass of hemorrhage moves when the conjunctiva is moved; with fracture of the anterior fossa the hemorrhage is subconjunctival.

3. With a conjunctival hemorrhage associated with "black" eye there is a posterior limit to the extravasation, whereas with fracture of the anterior fossa there is no such limit and the hemorrhage tends to be fan shaped, with the handle of the fan toward the iris.

4. With fracture there is a parallelism between the edema and the amount of blood in the eyelids; that is, the greater the edema, the greater the amount of blood by inspection. With "black" eye with pronounced edema there is relatively little blood.

24. Benedict, W. L.: Sarcoidosis Involving the Orbit, Arch. Ophth. **42**:546-550 (Nov.) 1949.

25. Rider, J. A., and Dodson, J. W.: Sarcoidosis, Am. J. Ophth. **33**:117-120 (Jan.) 1950.

26. Bodian, M., and Lasky, M. A.: Sarcoidosis of Orbit, Am. J. Ophth. **33**:343-353 (March) 1950.

27. Knapp, F. N., and Knoll, W. V.: Sarcoid of Orbit, Tr. Am. Ophth. Soc. **47**:147, 1949.

28. Junior, L.: Ocular Cysticercosis, Arq. Inst. Penido Burnier **8**:13-64 (June) 1949.

29. King, A. B., and Walsh, F. B.: Ocular Signs of Head Trauma, Am. J. Ophth. **32**:191-206 (Feb.) 1949.

5. With fracture the blood in the eyelids almost always is first seen at the medial border of the lower lid and gradually suffuses along the lids. It rarely joins the lesser suffusion in the upper lid at the outer canthus.

6. With fracture the conjunctivas usually appear clear when the lids are everted, whereas with "black" eye they are edematous and discolored.

Trauma or surgical procedures may result in emphysema of the orbit, a sign which, as King and Walsh [29] point out, is a helpful diagnostic criterion. Localized emphysema of the orbit may follow tooth extractions or operations on the paranasal sinuses. Air readily finds its way into the orbit when the lamina papyracea of the ethmoid bone is fractured. Increased intranasal pressure, such as that produced by sneezing and coughing or during "politzerization" of the eustachian tube, as observed in one of my own cases, forcibly propels more air through the fracture or the dehiscence of the lamina. This air reaches the eyelids, and the air is behind the septum orbitale to give (*1*) proptosis and narrowing of the palpebral fissure (emphysema of the lids with the air in front of the septum orbitale does not produce proptosis or pronounced narrowing of the palpebral fissure) and (*2*) orbital emphysema, apparent in roentgenograms.

Retrobulbar hematoma usually is of little consequence and absorbs in a few days with use of pressure bandage. However, in Wüst's [30] case the hemorrhage was produced after traumatic compression of the thorax and resulted in proptosis and amaurosis. He obtained prompt disappearance of these symptoms by entering the retrobulbar space through the maxillary sinus, with removal of the floor of the orbit. Falls, in a personal communication, noted his experience with permanent amaurosis following preoperative retrobulbar injection of procaine, which resulted in retrobulbar hematoma.

Retrobulbar injection of alcohol promises to be a more frequently used therapeutic aid in the control of intractable ocular pain. Weekers and Roussel,[31] Kornblueth [32] and Maumenee [33] have stated that the retrobulbar injection of 1 cc. of *2* per cent procaine hydrochloride followed by 1 cc. of 95 per cent ethyl alcohol will control ocular pain for one to three months. In neither blind nor partially seeing eyes has any

30. Wüst, K.: Treatment of Imminent Optic Nerve Atrophy Due to Retrobulbar Hematoma and Surgical Access to the Retrobulbar Space, Klin. Monatsbl. f. Augenh. **114**:140-144 1949.

31. Weekers, R., and Roussel, F.: Experimental and Clinical Researches on the Action of the Retrobulbar Injection of Alcohol, Ophthalmologica **118**:115-126 (Aug.) 1949.

32. Kornblueth, W.: Effect of Retrobulbar Alcohol Injection on the Eyes of Experimental Animals, Am. J. Ophth. **32**:781-792 (June) 1949.

33. Maumenee, A. E.: Retrobulbar Alcohol Injections, Am. J. Ophth. **32**:1502-1508 (Nov.) 1949.

permanent complication followed the injection. Injection of alcohol into peripheral nerves relieves pain by interrupting the transmission of the nerve fibers. Injection into sensory ganglions, on the other hand, destroys the ganglion cells and causes permanent anesthesia of the area supplied by the nerve. Permanent anesthesia of the eye is not produced by retrobulbar injection of alcohol, for the ganglion cells of the sensory nerves from the eye are located in the gasserian ganglion and not in the orbit. The parasympathetic motor nerves to the pupil and ciliary body are interrupted to some extent after retrobulbar injection of alcohol. Contraction of the pupil and accommodation, however, return within several weeks. The optic nerve is apparently protected to a considerable extent by its sheath from the effects of the alcohol.

Kornblueth [32] and Maumenee [33] have found that corneal transplants do very poorly when they are grafted into eyes of rabbits which have previously received retrobulbar injections of alcohol. The rate of the mitosis in the epithelial and stromal cells is reduced. This suggests that retrobulbar injection of alcohol might be detrimental to healing of large corneal ulcers.

Injections of alcohol did not reduce the ocular tension in absolute glaucoma, but Weekers and Roussel [31] reported that the tension is reduced in some patients with acute congestive glaucoma. No beneficial effects, other than relief from pain and blepharospasm, have been noted from the injections of alcohol.

Gifford [34] finds that motor block of the extraocular muscles by deep orbital injection of procaine above and below the optic nerve is advantageous during an intraocular operation. The only disadvantage of this method over the usual retrobulbar injection of procaine is a greater risk of retrobulbar hemorrhage.

The use of hyaluronidase with local anesthesia in ophthalmology was introduced this year by Atkinson.[35] It is known that in animal tissue hyaluronic acid seems to bind water in interstitial spaces and to hold cells together in a jelly-like matrix, which obstructs diffusion. The addition of hyaluronidase causes a rapid dispersion of fluid when injected into tissues. The rapid dispersion is brought about by a depolymerization and hydrolysis of the hyaluronic acid gel. The reduction in viscosity removes one of the barriers to diffusion of fluid and allows permeation of the tissues more rapidly and widely.

Atkinson [35] reports on 109 eyes in which an anesthetic solution containing hyaluronidase was injected before operation. The surgical

34. Gifford, H., Jr.: Motor Block of Extraocular Muscles by Deep Orbital Injection, Arch. Ophth. **41**:5-19 (Jan.) 1949.

35. Atkinson, W. S.: Use of Hyaluronidase with Local Anesthesia in Ophthalmology: Preliminary Report, Arch. Ophth. **42**:628-633 (Nov.) 1949.

procedures included minor operations on the lids, cataract extraction, enucleation with implants and operations for glaucoma, retinal detachment and strabismus. With the addition of hyaluronidase to the injections of an anesthetic solution of procaine and epinephrine, there was greater diffusion of the anesthetic, anesthesia occurred more rapidly and lasted as long, there was less ballooning of the tissues and the area of anesthesia was greater. More effective akinesia of the orbicularis and extraocular muscles was obtained. Hypotony was pronounced after cone injections and was occasionally sufficient to make the cataract extraction more difficult, but safer, and the vitreous was less likely to present. Ischemia due to the epinephrine was quickly followed by hyperemia of brief duration. The eye frequently became red after the cone injection.

Malignant exophthalmos continues to occupy a prominent position in the ophthalmologic literature. That this condition is relatively unusual is illustrated by Ryan's [36] finding of only three cases of mild thyrotropic exophthalmos in a series of 1,001 cases carefully selected for thyroidectomy. De Grósz [37] suggests that the name myopathia exophthalmica be used to stress the muscular origin of the diplopia and that the name malignant exophthalmos, which falls into the same category of thyrotropic exophthalmos, be reserved for the type showing a progressive character, involving the necessity of extensive surgical intervention on the lids and orbit to maintain the integrity of the eyeball.

Curtis, Cawley and Johnwick [38] have reported on the association of progressive (malignant) exophthalmos and localized myxedema. They cite eight cases to illustrate their contention that progressive exophthalmos and localized myxedema are allied manifestations of the same underlying disorder, namely, an excess of thyroid-stimulating hormone. Localized myxedema is always associated with toxic diffuse goiter, and thyroidectomy and thiouracil therapy usually initiate their onset. If a large portion of the thyroid cells are removed surgically, or if the cells of the thyroid gland respond to the stimulus of the thyrotropic hormone, most of the thyroid-stimulating hormone remains active and progressive exophthalmos develops. Similarly, the production of localized myxedema, of bilateral oval, indurated, yellowish brown, pigskin-like plaques, can be attributed to an excess of the thyroid-stimulating hormone limited to the anterior surface of the legs.

36. Ryan, H.: Thyroidectomy and Thyrotropic Exophthalmos (Exophthalmic Ophthalmoplegia): A Review of 1,001 Thyroidectomies, Brit. J. Ophth. **33**:769-773 (Dec.) 1949.

37. de Grósz, S.: Myopathia Exophthalmica, Acta ophth. **28**:1-6, 1950.

38. Curtis, A. C.; Cawley, E. P., and Johnwick, E. B.: Association of Progressive (Malignant) Exophthalmos and Localized Myxedema, Arch. Dermat. & Syph. **60**:318-337 (Sept.) 1949.

Smelser and Ozanics [39] have shown that the injection of extracts of the anterior lobe of the pituitary into thyroidectomized guinea pigs produces an exophthalmos and an edematous condition of the orbital and some other fat tissues. Fat which is unaffected in its normal location by the injection of such extracts remains unaffected when transplanted to the orbit. Fat tissue which is affected in extract-treated animals also becomes edematous when transplanted to the orbit of appropriately treated animals. These findings strongly support the concept that the condition of the fat tissues found in exophthalmic guinea pigs is due to basic characteristics of the tissues and/or its vessels, rather than to its location or the peculiarities of its site, such as lymphatic drainage.

Franceschetti and Klein [40] and Waardenburg [41] have, during the past year, made outstanding contributions to our understanding of the multiplicity of manifestations that the mandibulofacial dysostosis may present. The complete syndrome consists of the following signs:

1. An antimongoloid oblique direction of the palpebral fissure.

2. A triangular form of the open palpebral fissure, because the lower lid is crooked at the temporal side, which conveys the impression of the existence of a separate link, as a third eyelid, between the other two.

3. Deficient formation of eyelashes in the lower lid.

4. A hypoplastic zygoma, sometimes with a gap between the zygoma and the frontal bone.

5. A hypoplastic mandible with defective formation of the chin.

6. Sometimes, dysplasia of the maxilla with a high palatine arch.

7. High root of the nose with large frontal sinuses.

8. Open bite and other dental irregularities.

9. Sometimes, macrostomia and blind fistulas along a line from the corner of the mouth to the ear.

10. Anomalies of the external ear, consisting in low implantation and dysplasias of the auricle, sometimes with atresia and other defects of the external auditory meatus, with conduction deafness.

Signs 4 to 8 are those typical of the dysostosis, but many incomplete and abortive forms are seen. The increasing number of cases reported clearly demonstrates the hereditary nature of this syndrome. Apparently, the syndrome is of genic origin and is transmitted in an irregular

39. Smelser, G. K., and Ozanics, V.: The Reaction of Various Types of Fat Transplanted into the Orbit of Guinea Pigs Prior to the Development of Exophthalmos, Am. J. Ophth. **32**:1557-1563 (Nov.) 1949.

40. Franceschetti, A., and Klein, D.: Mandibulo-Facial Dysostosis: A New Hereditary Syndrome, Acta ophth. **27**:143-224 (Aug.) 1949.

41. Waardenburg, P. J.: Mandibulofacial Dysostosis, Ann. d'ocul. **182**:318-325 (April) 1949.

dominant nuele. From his observations, Franceschetti [40] feels that the condition is due to an unstable gene of occasional pleiotropic (polyphenotypic) effect, especially on the skeletal system.

Continual modifications and improvements have been made in the integrated orbital implants in an attempt to overcome the frequent extrusions, conjunctival discharge, tilting and exposure of the tantalum mesh. Guyton [42] has reviewed enucleation and allied procedures up to the present time and has covered the subject so exhaustively that further review of this subject would be useless. Suffice it to say that a tabulation of the results obtained with the various semiburied implants and exoplants is being made but that at present superiority for any one or the other procedure cannot be claimed.

As yet no reports have appeared in the literature on the use of adrenocorticotropic hormone (ACTH) or cortisone (17-hydroxy-11-dehydrocorticosterone; formerly called compound E) in the study or treatment of orbital diseases. We can look forward this year to a new, exciting chapter to be written from their use. Much new information should be gained referable to thyrotropic exophthalmos and other collagenous conditions, which now give the ophthalmologist so much trouble.

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42. Guyton, J. S.: Enucleation and Allied Procedures, Am. J. Ophth. **32**:1517-1534 (Nov.) and 1725-1734 (Dec.) 1949; **33**:283-290 (Feb.) 1950.

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Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

Edwin B. Dunphy, M.D., President

Merrill J. King, M.D., Secretary-Treasurer

Regular Meeting, April 21, 1948

CASE PRESENTATION

Patients were presented showing the following conditions: (1) traumatic calcification of the lens with faulty light projection; (2) corneal ulcer, believed to be of rosacea type, which improved markedly with the intramuscular use of the vitamin B complex; (3) hyperplastic conjunctivitis associated with ectropion; (4) corneal ulcer and vernal conjunctivitis with atopic eczema; (5) bilateral glaucoma and cataracts associated with senile psychosis; (6) serous retinitis in a young man with onset two weeks after a blow on the head.

PRESENTATION OF PAPERS

Glaucoma. DR. PAUL A. CHANDLER, Boston.

In this paper, the fifth of a series, on the diagnosis and treatment of glaucoma, the author discussed the type of glaucoma that is due to swelling of the lens, that associated with dislocation of the lens and that following extraction of the lens. Glaucoma from swelling of the lens should be treated with intensive miotics (4 per cent pilocarpine nitrate) prior to operation. Extraction of the lens in cases of this type should be done with a broad iridectomy. Glaucoma from dislocation of the lens is usually due to blockage of the pupil, either by the lens or by vitreous, and may frequently be relieved by mydriatic therapy or by transfixion of the iris. The latter procedure is best carried out in the extreme periphery of the iris, as here one is least apt to encounter vitreous. When the glaucoma is not due to block of the pupil, the cause is presumably angle block, and treatment should be with miotics and filtering operation. Whether or not removal of a dislocated lens is indicated depends a great deal on how much vision is interfered with. Loss of vitreous and secondary separation of the vitreous are such frequent consequences that conservative treatment is usually advisable. Glaucoma following removal of the lens, whether by needling or by linear extraction, is most often due to pupillary block by posterior synechias and vitreous. It is therefore inadvisable to begin needlings until the patient is of an age at which the pupil may dilate readily, and peripheral iridectomy or iridotomy is indicated, with repeated needlings. Similarly, with linear extractions it is of prime importance to do a peripheral iridectomy and to keep the pupil dilated in the postoperative period. Glaucoma following cataract extraction is likely to occur in eyes in which there has been loss of vitreous or prolapse of iris, but the commonest predisposing cause is delayed reformation of the anterior chamber (that is, two or more days after the operation). When the anterior chamber has been flat for one week

after operation, it is wise to inject air, and possibly to draw off subchoroidal fluid from the sclera.

Kodachrome Atlas of External Malignant Growths of the Eye, Showing Lesions Before, During and After Treatment with Radiation, Radical Surgery and Thermophore. Dr. Brendan D. Leahey, Lowell, Mass.

A series of kodachrome slides were projected showing various tumors of the lid and conjunctiva, together with the means by which they may be removed. The author expressed himself in favor of surgical removal when the tumor was in a region of loose tissue but recommended irradiation when the defect could not be covered by adjacent tissue.

Hypercalcemia and Pathogenesis of Band-Shaped Keratopathy. Dr. David G. Cogan, Boston.

The author presented a series of 16 cases in which there was hypercalcemia with subepithelial opacities in the cornea and conjunctiva. The causes of the hypercalcemia were hyperparathyroidism, sarcoidosis, vitamin D intoxication and excessive calcium intake. In addition to the ocular changes, most of the patients had evidence of nephrocalcinosis, and many had renal insufficiency. The author described the pathologic changes in band-shaped keratopathy and suggested that the condition represented a supersaturation type of calcification.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Wendell L. Hughes, M.D., *Chairman*

Isadore Givner, M.D., *Secretary*

Oct. 18, 1948

CASE REPORTS

The Eye in Teratomas. Dr. Goodwin M. Breinin.

This paper was published in full in the March issue of the Archives, page 482.

DISCUSSION

Dr. Abraham Kornzweig: This condition is a rare anomaly, and one that I have never seen before. There was no lens in the slide of the case presented. At one time it was thought that an optic anlage could not exist unless a lens was present with the optic vesicle. The lens is the result of a reaction of the surface ectoderm which is adjacent to the optic vesicle. It is a nonspecialized portion of this ectoderm. If there is any surface ectoderm in the vicinity of the optic vesicle, that tissue will undergo lens formation. Apparently, inside the teratoma, ectodermal tissue was not adjacent to the optic vesicle, or not sufficiently near to form a lens. The absence of the lens does not refute the diagnosis that this structure is an optic vesicle.

Optic vesicles are all invaginated. Invagination of the primary optic vesicle is an inherent function. No matter where the tissue may be, it will always undergo invagination. This has been proved by trans-

plantation experiments. That portion of the embryo which is going to be an eye when transplanted to other parts, in the region of the abdomen for example, goes on to form an optic vesicle and a secondary optic cup.

The eye in the teratoma shown resembled that seen in a 7 week old embryo.

A Simple and Efficient Cataract Suture. Dr. Joseph Laval.

This paper was published in the August 1949 issue of the Archives, page 189.

DISCUSSION

Dr. Charles A. Perera: Theoretically, the ideal corneoscleral suture is an appositional one, and the safest corneoscleral suture is one placed before the eyeball has been opened, because the structures are firm and the danger of damage to the interior of the eye and dislocation of the lens is absent. The next safest suture is one placed after a small incision has been made. For years I have been using a suture similar to that described by Dr. Laval. A small conjunctival flap may be made, a large one or a sliding flap. After a keratome incision the silk sutures (two) are placed near the extremities of the incision so that they bite into the apposed margins of the incision. The sutures are looped out of the way, and the section is completed with scissors. A cross section of the suture shows that the anterior third of the corneoscleral incision is included in the suture. At the termination of the operation the conjunctival flap is further closed with interrupted silk sutures.

Dr. John M. McLean: Although originally I used a single corneoscleral suture, I now always use two sutures. For over ten years I have used the method which Dr. Perera described in the rare instances in which I start with a keratome section.

PAPERS OF THE EVENING

Use of Hemostats in Ophthalmology. Dr. Moacyr E. Alvaro, São Paulo, Brazil.

Hemorrhages are the result of changes in the walls of the blood vessels, in the capillary endothelium or in the blood itself.

Nonsurgical bleeding occurs under four types of conditions: (1) normal blood vessels, normal blood, normal bleeding time and normal coagulation time; (2) damaged capillary walls with normal blood vessels, normal blood, normal bleeding time and coagulation time; (3) damaged blood vessel walls and normal blood and normal coagulation time, but prolonged bleeding time; (4) abnormal blood with normal blood vessels and normal bleeding time and delayed coagulation time.

In hemorrhages corresponding to types 1 and 2 the test for capillary resistance should be made. The result will be positive in cases of deficiency of vitamins C or P. Hemorrhages corresponding to type 3 occur in purpuras and vascular disease. The treatment is etiologic and consists of elimination of possible foci, splenectomy (in cases of primary purpuras) and blood transfusions. Hemorrhages of type 4 may be caused by deficiency of prothrombin, and the diagnosis should be made by the prothrombin test. The condition may be caused by intestinal and biliary disturbances and damage to the liver, or it may be congenital. Retinal hemorrhages in infants at birth can generally be prevented by giving a preparation of vitamin K to the mother before labor.

The different types of ocular hemorrhage, such as ecchymoses, subcutaneous hemorrhage, subconjunctival hemorrhage and hemorrhage of the uveal tract—the iris, ciliary body and choroid—were discussed. When there is reduced resistance of the capillary walls, preventive or curative vitamin P therapy should be given. In thrombosis of the central retinal vein and papilledema, treatment should be directed toward reestablishment of circulation, with the use of heparin, dicumarol or roentgen rays, which act as vasodilators.

The physical means used in ophthalmology for the management of surgical bleeding are heat, aspiration and absorption. The chemical means should include the use of vasoconstrictors and substances increasing capillary resistance and general or local application of the elements needed normally for blood coagulation or of one or more specific elements found lacking. General or local measures should include the use of tissue extracts, papain, staphylase and some snake venoms. Some of the snake venoms act directly on fibrinogen, changing it into fibrin; such a substance is the venom of Bothrops jararaca, of which 1 mg. in 1 cc. of water previously detoxicated by heat at 150 F. for fifteen minutes speeds up blood coagulation when used either intravenously or locally.

Preoperative and postoperative measures for hemostasis were briefly reviewed, as were methods of hemostasis during operations, special emphasis being placed on the influence of sutures, incision and iridectomy on hemorrhages in the operation for cataract.

DISCUSSION

Dr. Daniel B. Kirby: As Dr. Alvaro has so well analyzed the factors productive of hemorrhage—the condition of the vessels, of the blood and of the patient—I shall not attempt to go over the same ground but shall bring out some practical points from my own experience. Conditions in which one may expect bleeding are as follows: (1) High systolic pressure. Nevertheless I have had successful results after sedation, rest and relief from emotional disturbances. (2) Fixed diastolic pressure over 110, particularly over 120 mm. of mercury. With such a pressure one may expect filling of the uvea on decompression of the eye by corneal section or sclerotomy, and hemorrhage in the posterior segment, even expulsive in character. (3) Gross enlargement or visibility of the vessels of the iris. (4) Metabolic disorders, such as diabetes. (5) Increase in prothrombin time.

It is for the last condition that vitamin K is valuable. I have not had enough personal experience with the venom of Bothrops. It acts to speed up clotting only when the vessel is cut or injured. It does not predispose to intravascular thrombosis, as vitamin K may do.

The bleeding and coagulation tests have never helped me very much. I wish there were a test which would give the bleeding potential of each patient before operation. I have tried incising the skin, as well as shaving off the cuticular layer to expose the arterioles, but I have not had conclusive results.

The immediate causes of surgical bleeding are: (1) direct injury to the vessels, as by injection or incision, and (2) indirect injury, by decompression.

To prevent the latter, slow evacuation of aqueous, particularly in cases of glaucoma, is advisable. I try to prevent injury to the vessels during the injection of the local anesthetic solution by inserting a little

fluid in advance of the needle, and I do not distend the tissues too much. I have given up retrobulbar injections, first, because I have found that anterior injections are as satisfactory for anesthesia, and, second, because retrobulbar injections do not give satisfactory akinesia of the orbital muscles and because the frequent occurrence of extravasation behind the deep fascia produces pressure which embarrasses the operator. It is true that real hemorrhages which cause delay in the operation to another time are rare. I had only 3 such cases, but in many others I was forced to do lateral canthotomy for relief of pressure. For some time I have used subconjunctival injections and injections under Tenon's capsule. Even with these, hemorrhages are frequent, but they do not cause pressure on the globe, and if hematomas form they may be opened and evacuated. The frequency of hemorrhages in the anterior chamber has proved my contention that posterior hemorrhages are frequent after retrobulbar injection. Hemorrhage from the conjunctival flap need not be as disturbing as hemorrhage from section of the limbus. I agree with Dr. Alvaro that if the section is not too deep there is less chance of embarrassing hemorrhage.

Hemorrhages in the iris may be avoided by iridotomy rather than by complete iridectomy. The greater and lesser circles of the iris need not be cut in the majority of cases of cataract, the round pupil being preserved.

Recurrent hemorrhages in the iris are now rare. They occur only in cases in which organic disease of the vascular tissue or blood disease exists.

Dr. Conrad Berens: I have selected as a first point for discussion the closure of wounds in cataract surgery. I agree with the conclusion drawn by Dr. Alvaro, which is fairly well accepted in the literature, that two appositional corneoscleral sutures are more effective than one in the prevention of postoperative hemorrhage.

Another important factor is whether the incision is in the cornea or in the sclera, and Dr. Alvaro mentions a shallow incision. To my mind, this is more important than the number of sutures employed. I firmly believe in the formation of a complete conjunctival flap in preventing postoperative complications and have been able to accomplish a corneal incision by carefully dissecting a narrow flap well down into the cornea. A special narrow cataract knife, with a straight back and straight cutting edge, is then used to make a subconjunctival incision in the upper third of the cornea. Before this method was used, the incisions were more scleral, and the incidence of postoperative hemorrhage in the anterior chamber was greater. After cataract extraction I have found that complete iridectomy apparently increased the incidence of hemorrhage in the anterior chamber, as compared with peripheral iridotomy. If iridectomy is performed in complicated cases, care should be taken to excise the iris tissue in an area as free as possible from blood vessels.

I believe that the electrodesiccation of all bleeding points has also been effective in controlling postoperative hemorrhage.

Another factor which was mentioned as important in the prevention of postoperative hemorrhage is study of capillary fragility. I should like to call attention to a simpler, and possibly more scientific, method than the positive pressure technic of Gothlin or Griffith's use of the sphygmomanometer cuff. The instrument used is named a petechiometer. It

consists of a plastic cup 2 cm. in diameter, with a magnifying glass on the bottom of the cup. The cup is placed, with the bottom up, against the inner side of the upper arm, and firm pressure is maintained on the top of the cup while the plunger is released. The plunger is so arranged that 10, 20 or 30 cm. of negative pressure may be obtained. The suction is maintained for one minute, and the petechiae are counted in five minutes. The absence of petechiae when the stop ring on the plunger is in the innermost slot when suction is produced means that the capillary fragility is greater than 10 cm. of mercury. One, but not more than two, petechiae indicates that the capillary fragility is under 10 cm. of mercury. The same procedure and interpretation of findings hold true when the suction is arranged for 20 and 30 cm. of mercury. It was determined by Franke (*Ztschr. f. klin. Med.* **135:** 283, 1938) that the capillary resistance on the outer surface of the upper arm at the level of the base of the heart ranged from 20 to 25 cm. of mercury. Examinations are made several weeks before operation, and when increased capillary fragility is found I prescribe rutorbin® (30 mg. of rutin and 200 mg. of ascorbic acid) three times daily. Calcium gluconate is administered intravenously, and from 2 to 10 cc. is withdrawn and injected intramuscularly. If improvement is not obtained, I have used ascorbic acid intravenously, with apparent success. However, I have not injected vitamin P intravenously and should like to know whether Dr. Alvaro has.

There are two other questions I should like Dr. Alvaro to answer. One is whether the roentgen treatments he advises for uveitis have had a beneficial effect when hemorrhages have been troublesome or whether this form of treatment is contraindicated in case of hemorrhage.

I should like him to suggest what he considers the best method of preventing expulsive hemorrhage. It is my impression that retrobulbar injections containing epinephrine have increased the incidence of expulsive hemorrhage. Is this correct?

DR. JOSEPH LAVAL: If one is afraid that iridectomy will produce hemorrhage, it is feasible and safe to inject thrombin topically into the anterior chamber before the iridectomy; I have done it on a few occasions and have had no bleeding.

DR. MOACYR ALVARO, São Paulo, Brazil: I have not so far used vitamin P intravenously. I have administered it only orally, giving 60 mg. a day, and I believe it should be used over a long period. One cannot expect an increase in capillary resistance by giving vitamin P for a few days. It must be given for months.

With regard to the prevention of expulsive hemorrhage, I really cannot say, Dr. Berens. I have read an article based on statistical data which seemed to prove that retrobulbar injections of tetracaine and epinephrine do not seem to influence the incidence of expulsive hemorrhage in one way or another.

In the roentgen treatment of uveitis, the dose of which should never exceed 80 r, I feel that it can never be harmful when there are hemorrhages.

Senile Macular Lesions. DR. RALPH I. LLOYD, Brooklyn.

The ophthalmoscope established ophthalmology as a specialty despite the conservative attitude of members of the medical profession. It is indispensable and has been brought to a high degree of perfection. With

monocular observation it is impossible to locate the depth of lesions unless the striate fibers of the nerve fiber layer are involved or the lesion is anterior to the retinal vessels.

Many important conditions never come to the laboratory unless they imperil the other eye or cause great pain. Ophthalmologists have been compelled to rely on the ophthalmoscope, and only recently have photographs and paintings of the fundi been available.

Observation of lesions over extended periods has amplified knowledge of lesions previously not well known, but the simplified binocular ophthalmoscope has come to be a most important instrument in diagnosis of diseases of the fundus. With this instrument the retina stands out in advance of the tapetum (pigment layer, lamina of Bruch and chorio-capillaris), which provides the color of the fundus. Despite the advantages of repeated examination and illustration and the binocular ophthalmoscope, one must speak cautiously until the laboratory report of the various stages of the disease is at hand.

The binocular ophthalmoscope will clearly show that a soft white spot, usually diagnosed as chorioretinitis, is really an elevation, which the ophthalmoscope will show to be exudate beneath the pigment layer. Many lesions of the fundus which have been given the status of entities are actually stages of senile degeneraion due to the effects of time on the elastic tissue of the choriocapillaries and the lamina of Bruch, as well as to a special vulnerability of macular tissues. The common effect of age on the fundus is atrophy of the pigment-bearing tissues and sclerosis of the choroidal vessels. This change may progress to an advanced stage, with but little serious effect on the vision, but a series of lesions occur in the eye, of which hole in the macula is well known. An exudate may collect in the macular area and strip the pigment layer from the lamina of Bruch. Such an accumulation appears as pseudotumor with more or less hemorrhage in the tapetum. The pseudotumor may change into a cyst, owing apparently to the clear fluid breaking through the pigment layer to appear beneath the transparent retina.

The exudate may organize and produce the "cotton wool" spots of Coats's disease (retinitis exudativa) or flatten down into the organized plaque of tissue covering the macular area, well known as Kuhnt-Junius disease or disciform degeneration of the macula. Occasionally the cyst spreads laterally, raising the retina of the neighborhood to make a flat detachment. The initial stage may be a hemorrhage which breaks through the pigment layer and, seen through the retina, receives the name of detachment of the choroid, subchoroidal hemorrhage or melanoma. Such a lesion requires immediate removal of the eye. Recent reports of cases of angioid stripes indicate that the pathology of this unusual condition is very similar to that of the senile states described.

Behr explained the appearance of exudate beneath the pigment layer as an original lesion of the lamina of Bruch and the organized tissue resulting from a metaplasia. Axenfeld, Verhoeff, Brown and Bertha Klien offer a much better explanation in their reports of serial sections, all showing eventually numerous breaks in the lamina of Bruch through which blood vessels from the choriocapillaries pass. I would plead for routine serial section of these eyes and also of areas of detachment, in order that much worth while information of many hitherto obscure conditions may be obtained.

DISCUSSION

DR. FRANK D. CARROLL: The differentiation from retrobulbar neuritis of senile macular degeneration in the early stages may sometimes be difficult if only the ophthalmoscopic appearance is considered. Early in macular degeneration there may be only fine pigment mottling, which is frequently associated with excellent vision. Therefore if vision is reduced and the macular involvement is questionable, the presence of the following signs is often helpful:

1. Correspondence of central scotoma to the ophthalmoscopic findings. That is, if the lesion involves the fovea and the area just below it, the scotoma will include the point of fixation and the area just above it. There is no connection with the blindspot. In retrobulbar neuritis, on the other hand, there is frequently a connection between the central scotoma and the blindspot. So-called tobacco or alcohol amblyopia is frequently confused with early macular degeneration. Both may occur in the same age group, and it is not uncommon to find some pigment mottling in the macula of patients of this age. In tobacco or alcohol amblyopia the scotomas are always bilateral; they are connected with the blindspot, and the densest part of the scotoma is usually between the point of fixation and the blindspot.

2. Positive scotoma. In macular disease the scotoma is frequently positive; in retrobulbar neuritis, it is usually negative.

3. Pain. In acute retrobulbar neuritis, pain around the eye and on movement of the eye and tenderness to palpation are common.

4. Metamorphopsia. This is rare in disease of the optic nerve and common in macular disease. The tests are simple. The patient may look at a door frame, at a square or at a circle. If the cones are spread apart, as they usually are with edema of the macula, there is micropsia. If the cones are crowded together, macropsia is present. Frequently there is an irregular distortion of objects. These all point to macular disease.

In summary, then, very early macular degeneration may be difficult or impossible to distinguish from retrobulbar neuritis on ophthalmoscopic grounds. However, in macular disease, the scotoma corresponds to the lesion suspected, a positive scotoma is present, no pain occurs and, finally, metamorphopsia is present.

Wendell L. Hughes, M.D., *Chairman*

Isadore Givner, M.D., *Secretary*

Regular Meeting, Feb. 21, 1949

Photography of the Red Reflex. DR. VIRGINIA LUBKIN (by invitation).

This paper was published in full in the April 1950 issue of the ARCHIVES, page 718.

Clinical Experience with Antistin® in Treatment of Allergic Conditions. DR. WARD L. MOULD, Hempstead, N. Y. (by invitation).

A series of 86 private patients with ocular allergy treated with antistin® was reported. Seventeen patients with palpebral urticaria were treated by intravenous injection of antistin® hydrochloride (100 mg.),

13 experiencing prompt relief. Two treated with antistin® drops (0.5 per cent) showed improvement, and 2 did not. Additional intravenous therapy was required to control symptoms in some cases.

Of 41 patients with hay fever, 39 obtained dramatic relief with 100 mg. of antistin® hydrochloride intravenously. Twenty-five of the 41 patients were given maintenance doses of antistin® hydrochloride by mouth (200 to 300 mg. daily), with no recurrences of the hay fever. Of 16 not given antistin® by mouth, 10 required additional intravenous therapy. Of 24 patients with drug allergies affecting the eyes, 14 were given antistin® intravenously (100 mg.); 6 showed improvement, and 8 did not. One-half the patients given drops for local use with no additional therapy were benefited.

A side reaction was observed in only 1 patient in the series—phlebitis in the vein selected for injection. This patient had had previous attacks of phlebitis. Caution should be observed in administering the drug intravenously. It must be given very slowly, and blood which clots in the syringe should not be injected.

Antistin® is a valuable drug in the treatment of allergic conditions of the eye; symptoms are usually relieved, and side reactions are uncommon.

DISCUSSION

DR. JAMES HENRY BARNARD (by invitation): A high percentage of good results has been obtained in this study. The reaction is rapid in its occurrence; this is much more than can be said for the slow, long-drawn-out immunization procedures now in common use. The study provides further evidence of the value of the antihistamine substances in allergic conditions of this type.

What is the mechanism of action with the so-called antihistaminic drugs? Should they be called antihistaminic? There is no neutralization of histamine by the material. It acts, rather, as a block on the nerve endings to prevent an adequate histamine response in various tissues, such as smooth muscle contractions. Is the reaction to histamine the whole process in the allergic response? Various workers have submitted evidence that after removal of neutralization of histamine a specific allergic reaction may be produced in various sensitized tissues by the introduction of the proper antigen.

In studying these antihistaminic drugs, I have used the antistin® only in the form of tablets and drops. Antistin® and the other antihistaminic drugs seem to act fairly similarly. There may be some difference in degree in the efficacy of the various preparations. The use of antistin® drops has not been very satisfactory in the eye, and the tablets, while helpful in treatment of urticaria, in hay fever and perhaps in the pruritic symptoms of eczema, have not been very satisfactory in relief of asthma and some other allergic conditions. It is possible that with the oral and local use of antistin® the medicament does not come in contact with the particularly affected tissues to the extent it does with intravenous administration.

The allergist is always worried about various types of constitutional reactions, since antigens given intravenously are often attended with danger. I am not implying that antistin® is truly an antigen, but there is the possibility of the production of a so-called azoprotein from the antihistaminic substance introduced. These azoproteins may be pro-

duced by almost any kind of chemical substance which fastens itself on to protein material, and this may take place in vivo. It is conceivable that a powerful antigen might thus be developed, and this possibility must be thought of in using antistin* intravenously. The literature shows that allergic reactions have been reported to various antihistaminic drugs. The side reactions to antistin* that Dr. Mould spoke of are not allergic, but there have been so-called allergic reactions to this substance, and one of the physicians at Roosevelt Hospital told of a patient who gave a positive reaction to a cutaneous test with antistin.* It would seem to me that in using this material intravenously great care must be taken to prevent the possibility of an azoprotein reaction. Such a reaction would be more likely to occur after one had given previous administrations of the drug and then allowed several weeks to elapse before giving another. It would seem worth while to make an intradermal test with at least 0.1 cc. of the material and see whether an immediate or a delayed reaction is produced. It also seems safer to dilute the 2 cc. of material to 10 cc., for 1 cc. could be given and, if nothing happened, 2 cc. could be injected slowly—perhaps 1 cc. the first minute, 2 cc. the next minute and 3 cc. the third minute, until the 10 cc. was used. In that way the physician would be better able to note any possible anaphylactic reaction which might be developing. Until more experience has been had with the drug, epinephrine and aminophylline should be at hand. The patient should be lying down to prevent any possible circulatory collapse which might complicate the picture and be confused with an anaphylactic reaction.

Dr. Wendell L. Hughes, Hempstead, N. Y.: This substance has been used a little over a year, and Dr. Mould mentioned that he had tried it on his family. I tried it out on mine, too. A dose of poison ivy prompted me to try the drug, and I think it lessened the itching a little, but not much. I noted no symptoms whatever after four injections. My wife, to whom I gave the drug for a severe allergic headache, did have relief from her headache, but she became unconscious for about fifteen minutes. She told me it was like going under an anesthetic. When she awoke, she found she was free of her headache. This relief has been repeated subsequently; with a slightly smaller dose (two thirds) and a longer period (ten minutes) for the injection, no syncope was experienced.

Dr. Mould and I thought that the drug might be used in cases of allergic blepharoconjunctivitis, in which there is sensitivity to drugs such as atropine, so we tried putting the atropine in the antistin* solution. As Dr. Mould has said, the results were equivocal; we could not determine whether the treatment was effective or not. In 2 cases it did seem to help, and in 2 others it did not. Much more investigation is needed on this subject. About two weeks ago a patient told me that after an injection of 100 mg. of antistin* hydrochloride she had had abdominal pain and cramps. We had given her the tablets to take at home; she had discontinued the tablets, and the cramps had stopped. I told her to wait a week and begin taking the tablets again; she did, and the symptoms recurred.

Dr. Frederick H. Theodore: Has this drug been used at all in cases of vernal conjunctivitis?

DR. WARD L. MOULD, Hempstead, N. Y.: I have had no experience with its use in vernal conjunctivitis, although there have been reports in the literature. It was difficult to interpret the results because the number of cases reported was not great. The consensus is that antistin® is effective in the condition.

Clinical Management of Ocular Syphilis. DR. BRITTAIN F. PAYNE, DR. JACOB A. GOLDBERG and DR. JOHN T. SIMONTON.

Syphilis has been recognized for many years as a major cause of ocular disability and blindness. In more recent times, the incidence of syphilis of the eye has diminished to such an extent that patients with the disease are viewed with some curiosity. This is true in New York and other areas of the United States, according to a personal communication from Dr. H. A. Holle, Regional Director, United States Public Health Service. In spite of its rareness, ocular syphilis still exists and warrants the same respect it received when it was a major cause of blindness. The purpose of this paper was to offer comment on the present management of ocular syphilis in clinics and hospitals and to offer suggestions for improvement.

An effort was made to determine the completeness of the individual charts, especially with respect to (*a*) personal history, (*b*) family history, (*c*) contacts, (*d*) laboratory tests, (*e*) follow-up studies, (*f*) disposition and (*g*) results of therapy. Other items on the charts were likewise analyzed and tabulated whenever it was deemed desirable.

The question of procedures to be followed led the authors to think in terms of standardization and simplification of record forms, so that checking of items might portray clinical findings, therapy, recommendations and other points.

DISCUSSION

DR. JACOB A. GOLDBERG (by invitation): As a representative of the Social Hygiene Committee of the New York Tuberculosis and Health Association, which aided in carrying through the project of making a study of 100,000 cases of diseases of the eye in 1937, I had some part in the preparation of this report.

Standards for the diagnosis and treatment of ocular syphilis need to be set up.

Retinitis Pigmentosa and Glaucoma. DR. S. GARTNER and DR. A. Schlossman.

Retinitis pigmentosa associated with glaucoma has been reported in 38 cases in the world literature. Eight new cases were presented in this paper. In these cases both eyes were affected with retinitis pigmentosa, and congestive glaucoma was monocular in 6 cases and binocular in 2 cases. Pathologic specimens in 3 cases from the Army Institute of Pathology were presented. They showed typical changes of retinitis pigmentosa and advanced glaucoma. It was emphasized that there was a paucity of pigment in the trabeculum of the angle of the anterior chamber.

The role of inheritance in retinitis pigmentosa and glaucoma was discussed. Several pedigrees from the literature were presented, and the familial nature of 4 of the cases was determined. The two diseases may be linked together in the same chromosome and form a single hereditary syndrome.

DISCUSSION

DR. CHARLES A. PERERA: I presented a similar case before this society in May 1938 (Retinitis Pigmentosa with "Hole" in Macula, ARCH. OPHTH. **20:** 471 [Sept.] 1938). Thirty-two cases were found in the literature. My patient, a woman of 24, had two attacks of uveitis in her left eye, with the later development of bilateral acute congestive glaucoma. Each eye was treated by a Lagrange sclerectomy with complete iridectomy. Miotics were used for one and one-half years and have not been needed since. The visual fields, constricted to 15 degrees from fixation, have remained unchanged.

The evidence for a constant factor in the association of retinitis pigmentosa and glaucoma is not convincing. Heredity and vascular disease certainly play a part at times.

DR. DAN M. GORDON: Present knowledge does not entitle one to consider retinitis pigmentosa with glaucoma as a clinical entity. About 300 cases of retinitis pigmentosa have been seen at the New York Hospital during the last three years. In that series were 6 or 8 cases with glaucoma. One is struck by the tendency of the glaucoma to appear at an earlier age than usual. In no case with both retinitis pigmentosa and glaucoma was there excavation of the disk; perhaps owing to the glial tissue over the nerve head, this condition is uncommon.

Kjerrumgaard (Retinitis Pigmentosa with Special Reference to Otologic, Neurologic and Endocrine Complications, *Acta ophth.* **26:** 55, [June] 1948), in his series of 150 cases of retinitis pigmentosa, did not report a single case of glaucoma under the head of "ocular complications." Unless one has a series of 1,000 or 2,000 cases, I do not believe that one can draw valid statistical conclusions.

Three conditions must be considered as associated with retinitis pigmentosa: nerve deafness; mental symptoms, ranging from personality changes to insanity, and endocrine disturbances. The Laurence-Moon-Biedl syndrome is one of the complete expressions of the latter. It is not fully realized that many incomplete endocrine forms are seen.

Patients with retinitis pigmentosa and glaucoma whom I have seen have done very poorly under surgical treatment.

Perimetric measurements in cases of retinitis pigmentosa uncomplicated by glaucoma may show defects of the nerve fiber bundles. Hence, the perimetric picture of glaucoma associated with retinitis pigmentosa is rather confused.

The authors stressed the occurrence of choroidal sclerosis in the cases from the Army Institute of Pathology. On this point, too, there is considerable confusion. Verhoeff (Microscopic Observations in a Case of Retinitis Pigmentosa, ARCH. OPHTH. **5:** 392 [March] 1931), in his pathologic sections of the eye of a man aged 64 who had had retinitis pigmentosa since childhood, noted no evidence of choroidal involvement and cited others who confirmed his observations pathologically. Certainly, with the ophthalmoscope, many eyes seem to show involvement of the choroidal vessels, and many do not. Many patients with retinitis pigmentosa have fairly normal-looking retinal vessels; others have severe, advanced changes in the retinal vessels.

DR. ADOLPH POSNER: With regard to heredity, it is not possible to arrive at any conclusions from statistics alone. Retinitis pigmentosa is associated with many diseases, and so probably is glaucoma from the

genetic point of view. Thus, the only cases which suggest a hereditary connection between the two diseases are those occurring in the same family. In one such family, now under observation, retinitis pigmentosa and glaucoma occurred together or in different siblings of the same family.

Dr. Samuel Gartner: The incidence of glaucoma in 3 per cent of cases of retinitis pigmentosa, as given by Dr. Gordon, is rather high, for the incidence of glaucoma in the general population is far under 1 per cent.

We could not see the disk in all our cases, but excavated disks were seen in some, and of 3 eyes that were studied histologically, all showed this condition. In presenting the combination of retinitis pigmentosa and glaucoma for consideration, our concern was that the glaucoma may be missed because the patient is going blind from retinitis pigmentosa.

I was struck by the occurrence of the choroidal sclerosis in these cases. I am familiar with the claim that the choriocapillaris is the first part of the eye to become defective and that retinal degeneration is secondary to this change. Verhoeff showed by the study of a case of an early stage that the choriocapillaris was intact and that the rods and the external nuclear layer degenerated first.

Diagnosis and Treatment of Epidemic Keratoconjunctivitis. Dr. Alson E. Braley (by invitation).

Isolated epidemics of keratoconjunctivitis have occurred since 1946. Very few of these epidemics have been associated with industrial plants; nearly all have occurred in individual clinics and ophthalmologists' offices. The clinical picture of the disease was similar to that seen in the epidemics in 1941 to 1943, except that many of the patients infected recently had a severer form of the disease. Pseudomembranes and wrinkling of the cornea and iritis were not uncommon complications of the disease.

During the recent outbreaks a virus has been isolated that appears to be morphologically similar to the virus isolated by Sanders and Alexander. Immunologically, the patients recovering from the disease show serum antibodies to both viruses. Patients lose their antibody titer to the virus in from two to seven years after recovery from the disease.

In the treatment of the disease convalescent plasma was tried locally, without much success. Aureomycin showed some promise and was used in the treatment of 51 patients. Twenty-three, or approximately one-half these patients, showed a shorter duration of the disease and a decrease in the number of corneal opacities. Only patients whose treatment was started early received any benefit. In the laboratory, aureomycin has some slight antibiotic effect on the virus.

Dr. Joseph John Fried: I have recently seen 27 cases of keratoconjunctivitis. The tearing has been described as present chiefly in the early morning hours. Later in the day the patients did not complain much of it. The pain was characterized as a cold pain; it was stinging, as though someone had put a piece of ice on the eye. In the epidemic of this year the tremendous swelling of the lower lid caused by the escape of blood and serum was remarkable. A number of the patients

gave the impression that they had been hit in the eye. The eyelid was heavily swollen with numerous suffusions, lasting two or three days; the disease did not give the impression of conjunctivitis so much as of trauma. In some cases the chemosis of the bulbar conjunctiva was so deep and intense as at first to suggest tenonitis.

A few patients seen in 1941 and 1942 had the corneal opacities in greater distribution in the pupil than in the periphery of the cornea, whereas in the epidemic of 1948, in which the corneal opacities were peripheral, or peripupillary, the visual disturbance or permanent visual damage was considerably less than that in 1941 or 1942. In a number of Dr. Braley's cases the lesions were fairly deep in the stroma, reaching Descemet's membrane; in my cases they were more superficial.

In alleviating the pain and discomfort, the application of atropine from the very first stage of the inflammation was beneficial. The application of quinine bisulfate ointment (2 to 4 per cent) as soon as the acute stage was over was found very helpful in hastening the clearing up of the corneal opacities and in rendering better visual acuity than would have been expected otherwise.

Wendell L. Hughes, M.D., *Chairman*

Isadore Givner, M.D., *Secretary*

Regular Meeting, March 21, 1949

Residents' Program

Bilateral Retinal Edema: Report of a Case. Dr. John T. Worcester (Manhattan Eye, Ear and Throat Hospital).

T. B., an Italian woman aged 33, had onset of the present illness three weeks prior to her admission (February 1949) with swelling of the lids of both eyes, the nose and the face. This was associated with general grippal symptoms. Two days later blurred vision and micropsia developed.

The patient had handled hair dyes and manicuring material for several years. Her hair had begun to gray four years previously. For two years she had been treated for acne rosacea. Two days before the onset of the disease she had cleaned a dress in a small closed room with a volatile cleaning fluid. She had been anemic for the past three months.

Physical examination revealed a healthy woman with slight graying of the hair. Vision was limited to perception of hand movements in each eye. Examination revealed keratic precipitates, with aqueous flare and cells in the aqueous. The lens and iris were normal, the vitreous was hazy and filled with exudate; the fundus reflex was yellow; the retina was diffusely edematous (there was a question of complete detachment of the retina or choroid); the disks were hyperemic, the margins indistinct and the vessels engorged. There was a central scotoma for blue.

The clinical course was afebrile; the fundi remained unchanged for three and a half weeks, when clearing began. Three weeks after admission she had episodes of tachycardia, headache, eructation, nausea and a feeling of fever. At the time of discharge the ocular findings were essentially the same except that the fundi were clearing. After her dis-

charge the fundi presented a typical picture of diffuse choroiditis with severe field changes, but practically normal vision.

The work-up of the case consisted in a complete study of the blood, urinalysis; determinations of the basal metabolic rate; bacteriologic studies; skin tests for such conditions as allergy, tuberculosis and brucellosis, and medical, gynecologic, neurologic and otorhinolaryngologic consultations. All were essentially noncontributory.

Therapy consisted in courses of penicillin, sulfadiazine, streptomycin and glucosulfone sodium (promin®), typhoid vaccine (given intravenously), tripelennamine (pyribenzamine®) hydrochloride and an autogenous vaccine. No apparent improvement was noted from any of these treatments.

Comment.—The case is suggestive of bilateral diffuse choroiditis. The condition may, in time, prove to be a variation of Harada's disease or the Vogt-Koyanagi syndrome.

DISCUSSION

DR. FRANCIS C. KEIL JR.: The most important part of the discussion revolves about the classification of the disease. The condition was systemic; the patient had a fever and was fairly sick. Her almost complete functional recovery is interesting in view of the initial severity of her symptoms. I think Harada's disease and the Vogt-Koyanagi syndrome should be considered in the diagnosis.

Ophthalmic Evidences of Subclinical Neurosyphilis. DR. NORMAN S. JAFFE (New York City Hospital).

It is possible to detect early invasions of the brain in syphilis by means of pupillography. In a large number of instances early, incipient Argyll Robertson pupils may be demonstrated by this method before the Wassermann reaction and the colloidal gold curve of the spinal fluid become positive.

In several cases chosen at random from the venereal clinic of the New York City Hospital the pupillary reflex showed early impairment to light in spite of an apparently normal spinal fluid. Thus, pupillography is a valuable aid in disclosing early cerebral involvement in syphilis.

Early damage to the midbrain in neurosyphilis is reversible in many cases. In 1 case presented notable improvement in the light reflex followed antisyphilitic therapy. There are other reports of such improvement in the literature.

Several cases were reported which showed that, contrary to the accepted view, the pupillary reaction to convergence is impaired early in neurosyphilis. Pupillographic studies show that the convergence reaction is almost always severely impaired by the time the pupil becomes immobile to light. Indeed, in 2 cases reactions the inverse of the Argyll Robertson phenomenon were reported.

DISCUSSION

DR. OTTO LOWENSTEIN: There can be no doubt that pupillography may be valuable in all cases of syphilis with normal cerebrospinal fluid in determining whether or not the disease is still progressive. One of the most demonstrative cases was also the first I ever saw.

A mother brought her 7 year old son to the hospital because he showed psychopathic symptoms. Examination of the child revealed definite signs of congenital syphilis. Following the old rule that there is no congenital syphilis in a child without syphilis in the mother, I examined the mother, who denied having had any venereal infection; she did not show any symptoms. I made pupillographic tests of the mother and found a transitory pupillary phenomenon, never observed before. It was in existence for only a fraction of a second, and therefore was not visible to the naked eye; although both pupils were equal under the condition of rest, anisocoria developed while the pupils contracted, the anisocoria becoming maximal at the peak of contraction. It disappeared when the pupils recontracted. At that time I was not able to determine the significance of this phenomenon, which later I called "dynamic anisocoria." It was clear to me, however, that it was organic in nature and certainly due to hypofunction of the third nerve on one side. Since I was convinced from the child's symptoms that the mother must have had a syphilitic infection I was inclined to refer this dynamic anisocoria to that assumed infection. I therefore recommended antisyphilitic treatment, but the mother refused because she did not understand why it should be necessary. However, a year later she returned to the hospital as a patient herself with all the symptoms of dementia paralytica.

This case became the starting point for that series which led to the detection of a great number of pupillographic symptoms preceding the well developed Argyll Robertson pupil and other familiar pupillary symptoms.

Penetration of Aureomycin into the Eye. Dr. Andrew deRoetth Jr. (Institute of Ophthalmology of the Presbyterian Hospital in the City of New York).

Experiments were carried out to determine the penetration of aureomycin into normal rabbit eyes. Aureomycin borate in 0.5 per cent solution was used for the corneal bath, for iontophoresis and for subconjunctival injection. After the corneal bath aureomycin was not detected in measurable amounts in the aqueous. Iontophoresis and subconjunctival injection produced low levels in the aqueous (0.1 to 0.2 microgram per cubic centimeter). Iontophoresis was fairly well tolerated by the eye, but subconjunctival injection was irritating to such an extent that it was considered contraindicated.

Aureomycin hydrochloride, 20 mg. per kilogram of body weight, was administered intravenously and intramuscularly, and 50 mg. per kilogram of body weight was used orally. Aureomycin did not penetrate into the eye in measurable quantities when given orally or intramuscularly. The cornea, sclera, iris and ciliary body, the aqueous and vitreous humors and the spinal fluid showed appreciable concentrations of aureomycin (0.05 to 3.8 micrograms per cubic centimeter or gram) after intravenous administration. An interesting feature of the intravenous method was the slow rate of disappearance of the drug from the ocular tissues (eight to twelve hours). As compared with other antibiotics, aureomycin was more irritating and penetrated less readily into the eye, but once it had crossed the blood-aqueous barrier it remained longer in the ocular fluids and tissues.

DISCUSSION

DR. LUDWIG VON SALLMANN: The usefulness and rationale of such laborious and careful investigations as Dr. deRoetth has reported are quite evident. The so-called drug-parasite-host relationship is influenced by two factors: (1) the concentration of the chemotherapeutic agent at the site of the lesion and (2) the length of time over which the organisms are exposed to the antibacterial action of the drug. The interplay of other factors in this relation of organism, drug and host is often obscure and certainly cannot be controlled readily.

This makes the knowledge of the distribution of the antibiotic, its appearance and disappearance curve, the most important and most logical basis for any therapeutic procedure. Experience obtained with the action of drugs in other parts of the body has limited value for the eye. The characteristics of an antibiotic—its molecular size, its physicochemical and chemical properties, which govern diffusion, permeability, absorption, excretion and specific affinities for the tissue constituents—must have a different meaning and a different mode of action under the varying conditions of parts of the body. This means that, for the purpose of ophthalmology, the investigations should be carried out on the eye. Furthermore, any new promising antibiotic—and aureomycin can be considered such—must be tested separately, because even closely related chemical substances, such as the various types of sulfonamides, do not follow the same pattern of distribution.

The prerequisite for the assessment of the practical value of such investigations is an understanding of the applicability of the experimental data to the human eye, and I should like to say a few words on this point. Previous work in this field has shown that there is no hard and fast rule, no constant, which will allow one to relate data obtained from the rabbit eye, for instance, to the human eye. In systemic therapy the difference in the permeability of the intraocular capillaries, especially the ciliary capillaries, in the rabbit and in man is a real stumblingblock, particularly so if the level of the drug found in the eye of the rabbit, as Dr. deRoetth has shown, is close to the minimal therapeutic level. In such a case it would be inadvisable to expect from the therapeutic success in an experimental infection a favorable course of a similar infection in the human eye, even if the organism has the same susceptibility to the antibiotic. In local therapy the difference in the thickness of the outer coats assumes prominence in the interpretation of the experimental result. However, with these reservations in mind, and with a generous margin of safety in the application of the results, experimental data may provide valuable information and give a clue to the most promising type of therapeutic approach in clinical cases. I do not doubt, therefore, that Dr. DeRoetth's investigations on the various types of administration of aureomycin will serve the purpose and prove of great interest to the clinician in infections in which he decides to use this antibiotic.

Pathologic Changes in Ocular Tissues Following Electrocoagulation: A Preliminary Report. DR. GERALD M. BRANOWER (Mount Sinai Hospital).

Normal rabbit eyes were subjected to penetrating and surface electrocoagulation (surgical diathermy) and the eyes enucleated at regular post-

operative intervals. The pathologic changes which appeared up to and including five days were primarily those of intense destruction and coagulation of tissues for both penetrating and surface diathermy. The uveal tract was more severely affected by both forms of diathermy than was the sclera. Penetrating electrocoagulation produced severer local destruction with the production of a hole and the occasional incorporation in the wound of both choroid and retina. Surface electrocoagulation gave a less intense local destruction effect, but the changes extended over a larger area of retina and uvea. The earliest signs of adhesive chorioretinitis were present, but with a minimal inflammatory reaction.

DISCUSSION

DR. HENRY MINSKY: Many men have worked in this field; as recently as February 1949, Marr, writing on electrocoagulation for the relief of glaucoma (Marr, W. G.: *Amer. J. Ophth.* **32:** 241 [Feb.] 1949), presented 3 enucleated eyes which showed microscopically similar pronounced changes after operation. One of the purposes of my investigation was to determine whether or not the application of surface diathermy was successful in producing sufficient atrophy of the ciliary body and inflammatory adhesions of the ciliary body to the sclera to cause an immobilization of the ciliary muscle in the meridian of the retinal hole. These factors are important in proving my theory of spontaneous retinal detachment, in which the sudden spasm of a portion of the ciliary muscle is blamed for producing the tear in a weak spot in the retina and hyaloid membrane (Minsky, H.: *J. Mt. Sinai Hosp.* **8:** 863, 1942).

In evaluation of the photographs presented, several points must be remembered: 1. This work is a preliminary report, since we have not completed the study of all the sections, many of which are being processed. Some of the animals are still alive. 2. What occurs in the rabbit eye does not necessarily take place in the human eye. 3. Many of these destructive changes would not be present in operations for detachment of the retina because the retina usually lies far away from the effective points of electrocoagulation. One must not assume that these dramatic changes necessarily occur in surgical procedures on the human eye.

Clinical Research on Various Drugs Used in the Preparation of the Patient for Operations on the Eye. DR. JOHN R. ROCHE (Bellevue Hospital).

A new concept and approach to the use of basal anesthesia in ocular surgery was discussed. The criteria for evaluation of a drug were (1) sedation; (2) analgesia; (3) anesthesia; (4) akinesia, palpebral and global, and (5) akinesia, basal or general. The new approach to anesthesia was made by the use of drugs in proper dosage for specific purposes. In attaining the first three criteria, clinical observations were made on the following drugs: choral hydrate, paraldehyde, bromides, morphine, meperidine (demerol®) and methadone, as well as on the commonly used barbiturates. The fourth and fifth criteria may now be met by means of curare. Experimental research work on curare, its effects and manner of use, was presented.

It was concluded that curare acts to bring the globes into the primary position and to hold them there in perfect quietness for a period suffi-

cient for cataract extraction. That this procedure is a safe and efficient adjunct to ocular surgery is substantiated by cases of ophthalmoakinesia caused by the drug.

DISCUSSION

DR. DANIEL B. KIRBY: Impressed with the necessity of a quiet eye in a quiet body for the delicate maneuvers of cataract surgery, I have felt it important to prepare the whole patient rather than the eye alone.

Cases have been seen in which palpebral akinesia failed to safeguard the eye from the effects of the forceful contraction of the orbital muscles. The retrobulbar injection failed to induce orbital akinesia and caused embarrassment through proptosis produced by retrobulbar extravasation. The superior rectus stitch may fail, and is even a hazard because of the powerful elevator action of the inferior oblique muscle. One does not care to have the patient look down; on the other hand, neither does one want him to look up forcefully.

Many complications occurring during operation are caused by the patient's not having been properly indoctrinated and in not having proper basal sedation, anesthesia, analgesia and akinesia.

As for the first point, probably the less indoctrination the better. The only thing required is that he have confidence that he is doing the right thing in having the operation, that he relax and take what comes He should not be held responsible for cooperation in the operation. He should have such deep sedation that his conscious apprehension is overcome. Every surgeon knows patients in whom this state seems impossible without general anethesia. Most patients, however, will respond satisfactorily to sedatives which depress the cerebral functions without the production of narcosis. The patient should be somnolent or sleepy. On the basis of clinical research, I prefer phenobarbital for its prolonged action and pentobarbital for its prompt and deep effect. I order phenobarbital ½ grain (0.032 Gm. three times a day; pentobarbital sodium, 1½ to 3 grains (0.097 to 0.195 Gm.) at night, and, in the morning, pentobarbital sodium, 1½ to 3 grains about two hours before the operation. I visit the patient in his room one hour before the operation. If the patient is still hypertonic, nervous and apprehensive, he needs further sedation. I then order phenobarbital sodium, 1 or 2 grains (0.065 to 0.130 Gm.) or pentobarbital sodium, 1 to 1½ grains, given by intramuscular injection. In some cases I also order meperidine hydrochloride, 50 mg., to be given intramuscularly. When the patient is on the operating table, the analysis of his condition is made again by talking to him, by testing him for rigidity, particularly of the muscles of the neck, by looking for incoordination of the ocular muscles and by watching his respiration. If the basal sedation is not satisfactory, intravenous administration of 25 to 50 mg. of meperidine hydrochloride is used. A total of 100 mg. of the drug need not be toxic. Meperidine has some sedative action and a definite basal analgesic action. Meperidine is particularly valuable if, when the injections for palpebral akinesia and local anesthesia are made, the patient is found to be hyperalgesic. Usually with this intravenous injection he will quickly become quiet; in fact, he may go to sleep for about fifteen to twenty minutes, during which time the operation may be completed.

It will be noted that in developing the sedation and analgesia of the patient I do not use massive doses of any one sedative. Rather, I com-

bine synergistic drugs as needed, after a proper lapse of time for the action of each. I stay within the safe range of the drugs, so that nausea, vomiting and a morbid state will not be produced. Of course, the local anesthesia must be profound. I administer the drug by instillation, and if the patient is not hypersensitive to tetracaine I add the hydrochloride of this drug in 0.5 per cent solution to the 2 per cent solution of procaine hydrochloride.

Finally, there are patients whose deep reflex of muscular spasm and rigidity remains after conscious control is lost. This is a familiar phenomenon to the general surgeon, who may find that the muscles are not yet relaxed after the patient has gone under general anesthesia, whether ether, thiopental or some other agent is used. Deeper narcosis is necessary to do away with the muscular rigidity and reactions to surgical manipulation or pain. This effect must be paid for in sickness, in physiologic response to the larger doses of the anesthetic. The same phenomena are present with local anesthesia when conscious apprehension and effort are abolished or almost gone. Rather than give more than a safe dose of a sedative and narcotic drug, I have found satisfaction with the use of small doses of curare for basal akinesia. Used properly, curare stills the eye, quiets the muscles in general, relieves respiratory disorders due to the fear neurosis and puts the quiet eye in the primary position. If it is used wisely and well, one need not be embarrassed by respiratory failure. Curare is a valuable adjunct in adding basal akinesia to the program I have given.

Dr. Joseph Laval: Recently a substance called mephenesin (tolserol®) has been used for patients who have muscular spasm due to arthritis with pain. Mephenesin produces relaxation of the muscles in these patients, with relief of pain. I have used mephenesin for twiching of the lids due to involuntary contraction of the orbicularis muscle, and the majority of patients have had definite relief of the symptom. In connection with Dr. Kirby's comment on the involuntary rigidity which persists in some patients and for which curare is used, it is possible that the new substance mephenesin, which has no toxic effect, might replace curare.

Dr. John Roche, Brooklyn: Mephenesin, of which Dr. Laval speaks, is used in the management of spastic conditions and the athetoid conditions of parkinsonism, and great benefit has been claimed for this method. In a short series of cases in the neurologic service of this hospital the effects were not in keeping with the good things that have been said about it in the literature. I have used this drug in attempting to get the effects obtained with curare, but as yet they do not approach the beneficial action of that drug.

Effect of Topical Use of Histamine on Intraocular Tension. Dr. Richard E. Markley (Brooklyn Eye and Ear Hospital).

Reference was made to statements in several textbooks regarding the effect of histamine in the eye.

An investigation on a series of 33 normal patients seen at the Brooklyn Eye and Ear Hospital was reported. In each subject the intraocular tension of both eyes was taken. A solution of histamine diphosphate (1:1,000) was then dropped in the left eye only, and tension in both

eyes was checked thirty minutes later. The tension in a majority of the histaminized (left) eyes became slightly higher than that in the control (right) eyes.

DISCUSSION

Dr. Mortimer A. Lasky, Brooklyn: The role of histamine in the body economy has been the subject of much speculation and investigation in recent years. Histamine is believed to act directly on the muscle fibers, causing marked vasodilatation. It is generally distributed in the body and is readily liberated during reactions to trauma and antigens. Nerve stimulation from an injury initiates antidromic impulses that descend along the nerve fibers to blood vessels, resulting in vasodilatation, increased permeability and transudation of fluid and proteins through the capillary walls.

It has been demonstrated by Friedenwald that histamine, after intraocular injection in animals, causes an increase in the intraocular tension, along with histologic changes which are associated with glaucoma.

"Aminoglaucosan," a synthetic substance related to histamine, was introduced by Hamburger (*Med. Klinik* **21**:1495 [Oct. 2] 1925). "Tenosin," a mixture of histamine and tyramine, was advocated as a means of treatment of glaucoma in 1928 by von Hofe (*Arch. f. Augenh.* **98**: 201 [Sept.] 1927. Both these drugs caused such severe reactions that they have been discarded, despite their excellent miotic action.

Some clinicians have introduced the idea of a relation between allergy and glaucoma. This, of itself, points indirectly to a histamine effect in the mechanism. Recently, rutin has been used as an additional therapeutic agent for glaucoma on the assumption that it reduces capillary permeability.

Dr. Markley notes that histamine produces miosis, even in eyes that are under the influence of atropine or homatropine. This is to be expected, for histamine acts directly on the smooth muscle fibers. However, the tendency to an increase in the intraocular tension in addition would cause one to hesitate in using histamine for its miotic action. (The miotics that are commonly used usually cause arteriolar constriction and in this way help to reduce the fluid content of the globe.)

Dr. Ludwig von Sallmann: I should like to ask Dr. Markley why he has not used a higher concentration of histamine. Hamburger gave 2, 7 and 10 per cent solutions of aminoglaucosan, a histamine preparation. It caused pain, but if a local anesthetic was given previously this disadvantage was not serious. Systemic damage was not reported.

Dr. Richard E. Markley, Brooklyn: The reason for using this concentration is that it is the strength used by the allergists.

Dangers of the Retained Blind Eye. Dr. Carey Leggett Jr. (New York Eye and Ear Infirmary).

Four cases were presented in which a melanoma of the choroid was revealed on histologic section of the blind eye. These cases demonstrated the importance of the question, "What should one do when presented with an old blind eye the condition of which does not permit conclusive examination?" One should not wait for the symptoms to develop, as they usually do, but should convince the patient that he would be better off with a prosthesis.

DISCUSSION

DR. JOSEPH H. KRUG: In an effort to consider the frequency of occurrence of malignant tumor in blind eyes, the most recent 1,000 enucleated eyes sectioned at the New York Eye and Ear Infirmary were studied. Eyes removed with the broad diagnosis of absolute glaucoma or of phthisis bulbi were included in the statistics, but such eyes in infants and children were omitted. In the great majority of eyes, judging by the pathologic report, there was sufficient disease of the media to preclude an adequate examination of the interior of the eye. Of the 1,000 eyes, 377, or 37.7 per cent, were removed with a diagnosis of absolute glaucoma; of these, 23 contained a malignant growth, which was suspected in 7 and unsuspected in 16. One hundred and eighty of the 1,000 eyes were enucleated with a diagnosis of phthisis or atrophy. In 2 eyes an unsuspected malignant tumor was found. The results were tabulated as follows:

Absolute glaucoma	377 (37.7%)
Absolute glaucoma with malignant tumor	23 (6.1%)
Tumor unsuspected	16 (4.2%)
Tumor suspected	7 (1.9%)
Phthisis or atrophy	180 (18%)
Phthisis or atrophy with malignant tumor	2 (unsuspected) (1.1% of phthisical eyes)

Of the malignant tumors, 2 were metastatic carcinomas, found in eyes with absolute glaucoma; 1 was a dyktioma, found in a phthisical eye, and the remaining 22 were malignant melanomas. Twenty eyes were removed on the bases of being blind with defective transmission of light, but in them no tumor was found. This precautionary diagnosis, of course, is entirely justifiable and cannot be critized in any way.

This study revealed that (1) malignant growths are more frequently found in eyes with absolute glaucoma than in phthisical eyes; (2) the malignant tumor may be metastatic, but is usually a malignant melanoma; (3) a tumor of neuroectodermal origin may in rare instances be found in phthisical eyes. Such a tumor may represent on attempted spontaneous cure.

The incidence of malignant disease in 6.1 per cent of eyes with absolute glaucoma is significant. The fact that 4.2 per cent of such eyes contained an unsuspected malignant growth is very significant.

Numerous explanations have been offered for the occasional discovery of malignant tumors in "blind eyes." At a meeting of this section in 1943, Dr. Reese suggested that a chronic inflammatory process in certain eyes not only might cause the progressive loss of sight, with ultimate blindness, but also might irritate the choroidal tissues sufficiently to result in a malignant transformation of a previously benign lesion. This explanation would seem to fit the case in which an eye has gradually become blind over a period of many years is found to contain a small malignant growth.

Another possible reason for the presence of an unsuspected malignant tumor in a blind eye is that the malignant growth itself has produced the sequence of events leading to blindness, either by inducing repeated attacks of secondary glaucoma or uveitis or by producing repeated intraocular hemorrhages. In each instance the ocular disease is attributed to the presenting disorder, and it is only when the process has progressed either to absolute glaucoma or to phthisis bulbi that enucleation is advised and a malignant mass is discovered.

Finally, at times an injury or the history of an injury to the eye is considered the initial step which leads to absolute glaucoma or to phthisis bulbi. This history of injury affords a convenient explanation for the ills which afflict or have afflicted the eye and may put the observer off guard. When adequate visualization of the fundus is not feasible, careful examination, especially transillumination, is neccessary if the ophthalmologist would avoid missing the diagnosis of associated intraocular tumor. Of course, the relation which the injury itself may have to the occurrence of a malignant growth is difficult to ascertain.

Whether every blind eye the interior of which cannot be adequately studied should be removed immediately is, in my opinion, debatable. Enucleation is certainly the safer procedure. That every eye should be most carefully transilluminated and reexamined at intervals of not more than a year is not debatable. Defective transmission of light should be an absolute indication for enucleation.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA (B.M.A.)

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Aug. 16-21, 1948

Perth, West Australia

John Cunningham Saunders. J. BRUCE HAMILTON, M.B., Hobart, Tasmania.

The author outlined the world situation at the beginning of the nineteenth century, when Napoleon was paramount in Europe and the Australian colonies were being founded at the other end of the world to forestall the expansion of his colonial empire. He noted the unsatisfactory state of ophthalmology at the end of the eighteenth century. Into this picture came John Cunningham Saunders, who under the aegis of Sir Ashley Cooper, founded the first eye hospital in London in 1804. He had two colleagues in this work, John Richard Farre and Richard Battley, who were fellow anatomists at Guy's Hospital.

Saunders was born on Oct. 10, 1773, and in 1795 he moved to London and dissected under Sir Ashley Cooper, whom he followed as demonstrator in anatomy. Richard Farre was born in Barbados in 1775 and came to London in 1792 to finish his studies. Battley was born at Wakefield in 1770 and did not come to London to study at Guy's Hospital until 1795.

On Oct. 1, 1804 Saunders, at Cooper's instigation, published a proposal for the institution of a "Dispensary for the Poor Afflicted with Disease of the Eye and Ear." Attached to the proposal was a testimonial of approbation of the physicians and surgeons of St. Thomas' and Guy's Hospitals. On Jan. 4, 1805, a meeting at the City Coffee House followed this proposal, and a resolution setting up the Dispensary was passed. This came into effect on March 25 of the same year.

In 1808 the name of the hospital was changed from the London Dispensary for the Relief of the Poor Afflicted with Disease of the Eye

and Ear to the Infirmary for Curing Diseases of the Eye. In January 1810 Saunders published an illuminating medical report showing the progress which the hospital had made in six years. Unfortunately, that year Saunders died of cerebral hemorrhage, and his place was taken by Benjamin Travers, John Farre remaining as a physician at the hospital and Battley as its secretary. A few years later Farre published the "Treatise on Some Practical Points Relating to Diseases of the Eye," which had been prepared by Saunders before his death. In the second edition of this work, published in 1816, Farre gave an outline of the life of Saunders, with comments on his work and a detailed account of the autopsy on Saunders' body performed by Sir Ashley Cooper.

After Saunders' death, much controversy arose as to the originator of the needling operation for congenital cataract; after considerable acrimonious discussion, however a special report was issued at the hospital stating, officially, that John Cunningham Saunders was the originator of the operation. Saunders' needle is still in frequent use. The author pointed out other ophthalmic activities, both in London and in Exeter, during the first two decades of the nineteenth century and then briefly described the progress of the hospital which Saunders had started. In 1822 the hospital was moved from its original site at Charterhouse Square to Moorfields, under the name of the London Ophthalmic Infirmary. Finally, in 1837, the name was changed, for the fourth time, to the Royal London Ophthalmic Hospital, by which name it became world renowned.

The references cited extensively in the paper should in themselves make pleasurable and instructive reading.

Ocular Signs of Intracranial Saccular Aneurysm. Dr. Frank B. Walsh, Baltimore.

Walsh discussed the ocular signs of intracranial saccular aneurysm. He classified intracranial aneurysms as arteriovenous, saccular and fusiform. Saccular aneurysms were classified on the basis of etiology, as follows: (1) miliary aneurysms, which, situated on smaller vessels, are usually in the substance of the brain; (2) mycotic aneurysms, which arise as the result of deposition of septic emboli; (3) post-traumatic aneurysms; (4) atheromatous aneurysms, and (5) congenital saccular, or "berry" aneurysms, with which the paper was particularly concerned.

Dr. Walsh described the symptoms and signs of intracranial arterial aneurysms and pointed out that saccular aneurysms provided ocular signs which were of value in topical diagnosis. These ocular signs were discussed in detail in relation to each important site of occurrence of aneurysms, case histories being given by way of illustration. Subclinoid aneurysms or aneurysms arising within the cavernous sinus usually did not account for changes in visual acuity or visual fields; they characteristically produced ophthalmoplegia and involvement of the trigeminal nerve. Supraclinoid aneurysms—for example, those arising on the carotid trunk beyond the cavernous sinus, from the junction of the posterior communicating artery and the posterior cerebral artery, as well as from the anterior cerebral and the anterior communicating artery—produced unilateral loss of vision, paracentral and junction scotoma and bitemporal hemianopsia. Posteriorly situated aneurysms had produced sixth nerve paralyses, cerebellar signs and choked optic disks. Aneurysms

involving the optic radiations produced hemianopsia. Those arising from any vessel in the circle, except possibly the anterior cerebral and anterior communicating arteries, might press on the optic tract; noncongruous hemianoptic defects had been observed in the visual fields of several patients with aneurysm.

Walsh described the possible surgical procedures and went on to discuss interesting points in anatomy and physiology which had been brought to light by a study of the ocular sign of aneurysm. The phenomenon of regeneration of the third nerve, the collateral circulation between branches of the external and the internal carotid artery and sensitization to acetylcholine following denervation were described.

In discussion, he stated that involvement of the sixth nerve was rare and, apart from posterior aneurysm, was associated with complete ophthalmoplegia following aneurysm of the cavernous sinus. Hemiplegia after ligation was found in all the series, but was not common in younger patients. Keith and Wagener had described prehyaloid hemorrhages, but Walsh had not seen such lesions in more than 25 per cent of his cases. They were probably due to venous compression. He had found that the supraclinoid and subdural spaces were potential spaces only, and he could not explain how blood was sometimes found in the latter in cases of supraclinoid hemorrhage. All hospitals had had tragedies with operations on the sphenoid sinus in which an aneurysm had been opened. The pain could not be mistaken for that of tic. It might be terrific, cutting, burning, tearing and often inconsistent, but lasted for hours in some cases. The site of the pain in Walsh's cases had been in the vicinity of the eye and in the frontal and temporal regions.

Myasthenia Gravis. Dr. Frank B. Walsh, Baltimore.

The first part of the paper, which dealt with diagnosis, was based on the observation of 125 cases of the disease and was illustrated by cases of particular interest. The second part was concerned with treatment, but only with regard to its effectiveness in the management of "ocular" myasthenia and the present status of thymectomy. In his summary, Walsh said that the pathogenesis of myasthenia gravis remains obscure. For a correct diagnosis of the disease, knowledge of the ocular signs was necessary, and the following principle of diagnosis was offered: In cases in which the condition is characterized by external ophthalmoplegia and a diagnosis other than myasthenia gravis is not crystal clear, a diagnostic injection of neostigmine is indicated. The addition of atropine (0.6 mg. to 1.5 mg. neostigmine) should never be omitted. The response to neostigmine was variable in his cases and sometimes required experienced observation. If the response was pronounced and reproducible, it almost certainly indicated the diagnosis of myasthenia gravis. In rare instances, the patient with myasthenia gravis might be essentially resistant to neostigmine. Walsh pointed out that responses to neostigmine may be obtained in conditions other than myasthenia gravis—bulbar palsy, amyotrophic lateral sclerosis, muscular dystrophy, congenital ptosis—but that such responses are weak and, at least in congenital ptosis, not reproducible.

He referred to a possible relation between myasthenia gravis and hyperthyroidism, which might ultimately be elucidated. In the discussion of treatment he stated that for ocular symptoms neostigmine was unsatis-

factory, except in occasional instances. It had been established that thymectomy had real value in some cases. Indications for its performance, however, were not clear, and further study was urgent. He stated that he would agree to the procedure if the patient wished it, for only by means of careful study could its therapeutic value be clearly defined. However, so long as the results with neostigmine were satisfactory, he would advise the patient to keep his thymus.

Retrolental Fibroplasia in Premature Infants. Dr. William Councilman Owens and Dr. Ella Uhler Owens, Baltimore (read by Dr. Frank B. Walsh).

The condition of retrolental fibroplasia in premature infants has been intensively studied at the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital during the period of 1945 to 1947 and subsequently. This investigation resulted in a considerable increase in knowledge of the course of the disease. It disproved current theories of the etiology without producing a new one, but it indicated further lines of investigation, some of which are already being followed at the Institute.

The condition was originally described by Terry in 1942. In the fully developed stage of a typical case, an opaque, vascularized membrane lies against the posterior surface of the lens. The globe is often smaller than normal; the anterior chamber is frequently shallow, and occasionally posterior synechias form. Elongated ciliary processes, appearing like the coarse teeth of a comb, can be seen behind the iris on the membrane in the extreme periphery of the dilated pupil. In premature infants both eyes are usually involved, but not always to the same extent. In some eyes the retrolental membrane may be incomplete and cover only a localized portion of the retrolental space. In others the membrane may be limited to the periphery of the anterior vitreous at the equator of the lens. In these cases a localized detachment of the retina often extends into the membrane. Terry suggested that the conditions represented an acquired hyperplasia of embryonic connective tissue in the meshwork of a persistent tunica vasculosa lentis. Reese and Payne suggested that the membrane was a hyperplastic remnant of the primary vitreous. Krause stated that it was part of a congenital encephalo-ophthalmic dysplasia—essentially a prenatal abnormality of the cerebral and retinal neuroectoderm.

At the Wilmer Institute the following study was made:

1. One hundred and twenty premature children whose birth weight was 4½ pounds (2,040 Gm.) or less, and who were born between 1935 and 1944, were examined. No case of retrolental fibroplasia was found.

2. Two hundred and fourteen children whose birth weight was 4½ pounds or less, and who were born between 1945 and 1947, were examined. None had retrolental fibroplasia at birth. All were followed for six months, during which period retrolental fibroplasia was observed to develop in 5. The incidence was 1.3 per cent in the group weighing 3 to 4½ pounds (1,307 to 2,040 Gm.) and 12 per cent in the group weighing less than 3 pounds.

3. Subsequent to 1947 further cases developed, making a total of 9. Retrolental fibroplasia developed in these cases between the ages of 2 to 5 weeks.

In these groups of infants the fundi were normal at birth. Before the onset of definite signs of disease the remnants of the hyaloid system had disappeared. The first sign of disease was angiomatous dilatation of the retinal vessels, followed by massive retinal exudation and the formation of a retrolental membrane.

Walsh commented on the investigations and pointed out how clearly they disproved the theories previously advanced to explain the condition. He further pointed out the increased interest in the disease on the part of pediatricians and the often extensive treatment given in an attempt to reduce the mortality of premature children, the therapy consisting in administration of high protein diets and large doses of vitamins, repeated blood and plasma transfusions, parenteral administration of amino acids, hormone therapy and prophylactic use of penicillin.

He suggested its possible relation to angiomatosis retinae or retinitis exudativa (Coats's disease). He cited the ocular findings, by Reese, in twins born three months prematurely. In one twin retrolental fibroplasia developed; in the other twin, who died at the age of 3 months, hemangiomatous tissue was observed on the surface of the retina of both eyes at autopsy. In one of the eyes, the hemangiomatous tissue was associated with detachment of the retina. It is possible that this pathologic picture may have represented an early stage of retrolental fibroplasia, although clinically it was not recognized as such.

He noted that Hess and associates found hemangiomas of the skin more frequent in premature babies than in full term siblings.

Glaucomatous Uveitis. N. M. MACINDOE, M.B., Sydney, Australia.

Four cases of glaucomatous uveitis were described. In each case acute glaucoma had been the presenting symptom, secondary to iritis, hidden cyclitis, early peripheral choroiditis and circumpapillary choroiditis, respectively. Treatment consisted in paracentesis of the anterior chamber, instillation of atropine drops and oral use of sulfadiazine, with successful results. It was warned that acute glaucoma in young persons may mask uveitis.

Neoplasms of the Eyelids. B. K. RANK, M.B., Melbourne, Australia.

Almost all known neoplasms occur in the lids, and, provided certain conditions are fulfilled, surgical excision offers the best guarantee of cure. These conditions were stated as follows: 1. The excision should be adequate. 2. Tissue loss is kept at a minimum and tension avoided. 3. The reparative procedure for any resultant defect is that best suited to the case. Rank discussed his experience with simple and malignant tumors.

DISCUSSION

DR. R. KAYE SCOTT, Melbourne, Australia: Dr. Scott could not accept the opinion that surgical excision was the treatment of choice for all malignant tumors of the lid. He expressed the opinion that such measures should be reserved for the small proportion of cases in which failure of nonsurgical therapy was evident or in which necrosis or delayed healing was seen. He described his methods of treatment with roentgen radiation and radium.

Recurrent Intraocular Hemorrhage. F. J. B. Miller, M.B., Adelaide, Australia.

The presenter discussed the prognosis and treatment.

R. Kaye Scott, M.B., Melbourne, Australia, reported his method of treatment with radium and the results obtained.

Congenital Glaucoma: A Report of Seven Cases. Dr. G. H. Barham Black, M.B., Adelaide, Australia.

After a brief reference to the incidence, etiology and diagnosis of congenital glaucoma, or hydrophthalmos, Black gave the histories of 7 patients treated by him or by his associates. Six of the 7 cases occurred during the last four years. The treatment and prognosis were discussed.

Results with Contact Lenses. Darcy Williams, M.B., Sydney, Australia.

This report was based on replies received in response to a questionnaire sent to 118 unselected patients fitted with contact lenses in 1946. Forty-seven patients had keratoconus, and 24, delayed mustard gas (2-chloroethyl sulfide) keratitis. The results were successful in 71 per cent of patients with bilateral keratoconus and in 45 per cent of patients with mustard gas keratitis.

The author concluded that persons with abnormal sensitiveness of the eyes, asthma, hay fever and allergic conditions of the conjunctiva were unsuitable for contact lenses. Attention was directed to the difficulties of providing a satisfactory lens in cases of monocular aphakia when the other eye was normal, and to the problem of corneal edema, which was not entirely solved. Improvements in types of contact lenses were mentioned.

Rubella Retinitis in Tasmania. J. Bruce Hamilton, M.B.; Frank Phillips, M.B.; T. R. Palfreyman, M.B., and D. H. Waterworth, M.B., Hobart, Tasmania.

Examination of 46 deaf children at the Tasmanian Institution for the Blind, Deaf and Dumb revealed that in no less than 29 the deafness was due to rubella in the mother during pregnancy. Thirteen of these 29 patients had retinitis, which varied from fine pigmentary stippling to gross pigmentary and colloid changes with waxy disks. Other congenital ocular defects, such as nystagmus, anisocoria and cataract, were found among these 13 patients, whereas no congenital ocular abnormalities were present in the 16 deaf patients without retinitis. The remaining 17 patients whose deafness was not associated with rubella had no congenital ocular abnormalities.

Role of the Ophthalmologist in Industry. A. L. Tostevin, M.B., Adelaide, Australia.

This paper was a sequel to the one given before the Ophthalmological Society in Sydney in September 1947. It outlined the activities of the Visual Hygiene Committee for the year and laid stress on the necessity for the cooperation of ophthalmologists with industry.

The incidence of injuries to the eye in Australia represented approximately 25 per cent of both lost time and minor injuries. Of this number, 90 per cent were due to burns and foreign bodies. It was stressed that the vast majority of such accidents could be prevented.

Results of Trephine Operation for Glaucoma. CLIFFORD COLVIN, M.B., Orange, Australia.

The results of trephination in 45 cases of glaucoma were reviewed. The percentage of successful results was higher when preoperative vision was better than 6/12. Complications and factors eventually leading to loss of vision were detailed.

Ophthalmology in General Medicine. GEORGE A. BREW, M.B., Melbourne, Australia.

The ophthalmologist tends to be isolated from general medicine, taking little interest in other branches of medicine. Perimetry affords an example of how methods of examination can be improved. A new type of Bjerrum screen illuminator was described. Cases of mutual interest both to the oculist and to the physician were discussed.

An analysis of findings in the retinal vessels in 2,000 cases was presented. Eight per cent of patients over 40 years of age consulted an ophthalmologist first, with a complaint of headache or ocular symptoms. Three methods of increasing the interest of medical men in ophthalmology were discussed.

DETROIT OPHTHALMOLOGICAL SOCIETY

Leland F. Carter, M.D., President

William S. Gonne, M.D., Secretary

Regular Meeting, Jan. 20, 1949

Comparative Ophthalmology of Vertebrates. DR. HERMAN D. SCARNEY.

This interesting and unusual paper consisted primarily of comments on a large number of kodachrome[3] illustrations, most of which were original photographs of animals, birds and fish taken by the author. Different types of lenses and pupils were shown in diagrams taken from various publications and were illustrated by actual photographs of the animals themselves.

In fish the notable features are a spherical lens, round pupil and iridescent iris. Amphibia have an oval pupil, iridescent iris, and a lens which is in contact with the cornea. The slowed retinal circulation in a hibernating bullfrog was observed with interest.

The iridal markings of the reptiles blend with the mottling or stripes of the skin. An anterior chamber separates the cornea from the lens. The pupil is either round or vertically elongated, and various amounts of pecten are exhibited. Lizards show medullated retinal nerve fibers, and the gila monster has no macula.

Birds have large eyes as compared with the size of the head; they have a round pupil and show marked, but variable, development of the

pecten, a highly vascular organ, whose function is either nutritive or regulatory of intraocular pressure. The nictitating membrane is transparent, providing protection and permitting vision under water. Some birds, such as the eagles, have a bifoveate macula.

Some mammals possess a nictitating membrane, but this, as in the albino rabbit, is thicker than in birds, is vascular and is not transparent. Various degrees of medullation of retinal nerve fibers exist. A tapetum is present in many animals and may be either fibrous or cellular. Pupils vary in shape from a vertical slit, as in the cats, to a horizontal slotlike opening, as in the ungulates. In some species the lens is entirely embedded in the vitreous. The retina of a number of animals is very similar to the human retina.

Atypical Retinitis Pigmentosa with a Female Carrier State. Dr. Harold F. Falls, Ann Arbor, Mich.

A man aged 32 complained of difficulty in reading in dim light and was found to have atypical retinitis pigmentosa. He showed pigmentary stippling about the macula, attenuation of the retinal arterioles, gliosis of the nerve head, cataractous changes in the lens, pigment changes in the retina and advanced choroidal atrophy. His mother showed a glistening reflex from the fundus, similar to that in the 2 cases of "human tapetum" reported by Ida Mann. Subsequent investigation of 72 members of this family, most of whom lived in Wisconsin and Minnesota, showed what is known as an intermediate inheritance, characterized by slight manifestations of the condition in the carrier females. Such a female passes the abnormality—in this pedigree, atypical retinitis pigmentosa—to 50 per cent of her female offspring. This type of heredity is unusual in that most sex-linked diseases do not show any evidence of abnormality in the females. The carrier females in this family had normal vision without night blindness, slight constriction of the visual fields and slight pigment clumping in the older members.

A family showing a similar pattern of inheritance has been reported by Fralick and Parker. Thirty-eight members were studied, the affected males showing choroideremia and the female carriers slight pigmentary changes without night blindness.

Of the many sex-linked diseases of the eye, six show mild features of the condition in the carrier females: red-green color blindness; hereditary optic atrophy (Leber's optic atrophy); retinitis pigmentosa with myopia; retinitis pigmentosa with choroideremia; choroideremia, and fundus albinism with nystagmus.

The various possibilities in inheritance patterns emphasize the importance of careful study of the family tree before one gives genetic advice. It is necessary to study the entire family, including the normal members, and to reject hearsay evidence.

An Interesting Diagnostic Problem, with Report of a Case. Dr. Edmond L. Cooper.

A white man aged 27 had uveitis, which began in a mild form with diminution of vision. The cause of the inflammation was obscure, and the disease progressed steadily in spite of treatment. The only abnormal finding in the physical examination was bilateral inguinal lymphadenopathy of 2 plus severity. Biopsy revealed chronic lymphadenitis of

undetermined character and no evidence of sarcoidosis. The diagnosis was neuroretinitis, retinal periphlebitis with retinal hemorrhage, iridocyclitis and secondary glaucoma. Eventually the eye was removed. The pathologic diagnosis was tumor, lymphomatoid in character, probably reticulum cell sarcoma. An inguinal gland which was removed early in the course of the disease was diagnosed as chronic lymphadenitis. A cervical lymph gland removed late in the course of the disease showed the tumor. The pathologic examination of a testis removed because of serious involvement showed small cell lymphocytoma.

An exact classification of the tumor in this case is impossible. It probably represents a reticulum cell sarcoma or a lymphosarcoma. However, other lymphomatoid diseases are so closely related and so overlap that exact differentiation is difficult. It is generally considered that Hodgkin's disease and the tumors of leukemia should be separated from lymphosarcoma; yet one cannot overlook the fact that in leukemia, particularly aleukemic leukemia, the uveal tract may be affected by a great infiltration of lymph cells, the infiltration of the iris being frequently nodular, and intense venous engorgement and retinal hemorrhages may occur. The diagnosis of reticulum cell sarcoma is accepted with reservations, since it is felt that aleukemic leukemia has not been ruled out.

Leland F. Carter, M.D., *President*

William S. Gonne, M.D., *Secretary*

Regular Meeting, Feb. 17, 1949

Practical Application of Bacteriology to the Diagnosis and Treatment of Inflammatory Diseases of the Eye. DR. JAMES H. ALLEN, Iowa City.

Certain bacteriologic procedures can be carried out in the ophthalmologist's office and have practical application in clinical work. Examinations of smears and scrapings of secretions and exudates from the lid margins, conjunctiva and lacrimal sac, from abscesses and from punctures of the anterior chamber are easily performed, but the culture of organisms is not strictly an office procedure. Except for a microscope, the necessary equipment is simple, only a platinum spatula, slides, source of flame, staining rack, stains in dropper bottles and a wash bottle being required. Only two stains are necessary for routine work: Gram's and Wright's, the latter being satisfactory for demonstrating the inclusion bodies in cases of virus infections. Two slides should be prepared from each specimen, for staining by the two methods. The Giemsa stain is less practical than the Wright, because it requires incubation at 37 C. for one hour. Differentiation of bacteria is based on the morphologic character of the organisms and their reaction to Gram's stain. Pathogenicity is not proved by the presence of an organism, but may be assumed if no other likely organism is found.

The gram-positive cocci are the Staphylococcus pyogenes group, streptococci, Diplococcus pneumoniae and Sarcina. In conjunctival smears these organisms all tend to be diplococcic, occurring either singly or in pairs. Staphylococci exhibit considerable variation in size in the same smear, whereas streptococci are rather uniform in size but on the average are smaller than staphylococci. D. pneumoniae is lancet shaped,

with the flattened sides opposed, and is narrower and longer than the staphylococci or the streptococci. Sarcina which produces conjunctivitis is gram negative, the gram-positive forms not being pathogenic. Cubical arrangement is characteristic. Gaffkya (Micrococcus) tetragena also occurs in groups of four, is gram-positive and is a non-pathogenic contaminant.

The Neisseria group is composed of gram-negative cocci which are morphologically indistinguishable from each other, so that smears are inadequate for differential diagnosis. They may be identified only by culture and fermentation tests with dextrose and maltose. A tentative diagnosis may be aided by the knowledge that Neisseria gonorrheae and Neisseria meningitidis are usually intracellular, whereas Neisseria catarrhalis is usually extracellular. Fortunately, infections by any of these bacteria respond well to the same medicaments.

The important gram-positive rods are those of the Corynebacterium group and the anaerobes. Corynebacterium diphtheriae is the only pathogen of its group but may be differentiated with certainty only by laboratory cultures. Corynebacterium xerose may be abundantly increased in any condition lowering the resistance of the conjunctiva, except during the peak of the acute inflammatory change. The organism is normally present in the conjunctival sac. Corynebacterium pseudodiphtheriticum (hoffmanni) is similar to C. xerose. Anaerobic bacteria occasionally cause the panophthalmitis following penetrating wounds of the eye. Such an infection by Bacillus subtilis, a large gram-positive rod, is the only proved condition in which it is pathogenic. Clostridium perfringens (welchii), the gas bacillus, may produce gas in the anterior chamber and violent panophthalmitis. Bacillus anthracis and Clostridium tetani may infect penetrating global wounds.

Mycobacterium tuberculosis and Mycobacterium leprae are shown by use of stains for acid-fast organisms. Myco. leprae is rare in this country.

Certain of the gram-negative rods may be tentatively identified by their morphologic characteristics. Hemophilus influenzae is seen in a short coccobacillary form in smears taken from the conjunctiva, but in culture it is a slender bacillus. It is a common cause of acute catarrhal conjunctivitis. The Koch-Weeks bacillus is possibly a strain of H. influenzae but is seldom, if ever, found in this part of the country. Hemophilus duplex, the Morax-Axenfeld bacillus, is also uncommon here. It is a long thick gram-negative rod, with a tendency to occur as diplobacilli and produces angular conjunctivitis and excoriation of the lid angles, blepharoconjunctivitis and marginal ulcers of the cornea. It may best be seen in scrapings from the lid margins or smears from the foamy secretions at the lid angles. The diplobacillus of Petit is morphologically identical with H. duplex and produces the same type of lesions, particularly marginal ulcers of the cornea. Zur Nedden's bacillus is also similar but is found only in Belgium and the Rhine valley. However, these two bacteria, although similar in appearance to H. duplex, do not require blood in the culture medium. Hemophilus ducreyi and Hemophilus pertussis are of little significance in ocular disease.

The other gram-negative rods are impossible to distinguish by the examination of smears. Among them are Klebsiella pneumoniae (Fried-

länder's bacillus), Pseudomonas aeruginosa (Bacillus pyocyaneus), Proteus vulgaris and members of the Brucella group.

Viruses vary in intracellular characteristics according to their sizes. The larger viruses localize in cytoplasm and produce inclusion bodies in that substance, whereas the smaller ones localize and produce inclusion bodies in the nucleus. With present methods of study the smallest viruses cannot be seen to produce visible bodies in cells.

Penicillin is usually an effective therapeutic agent against the gram-positive and gram-negative cocci and the gram-positive bacilli, except the mycobacteria. It should be used in conjunction with serum in infections with C. diphtheriae. Penicillin is ineffective against gram-negative rods.

Streptomycin is highly effective against gram-negative bacilli, either by parenteral or by local use. Locally it is administered in a solution of 1 Gm. per 10 cc., 1 drop being administered each hour during waking hours. By parenteral injection, the dose is 0.5 to 1.0 Gm., given twice daily. This dosage is also effective in treatment of tuberculosis.

Aureomycin should be used against gram-negative bacilli if streptomycin is ineffective.

Since the introduction of the sulfonamides, gonococcic and meningococcic infections of the eye have been much less serious. Penicillin produces rapid sterilization of the conjunctiva in these infections except in the case of a few nonsusceptible strains. Either sulfonamides or penicillin or both should be used.

Pemphigus, allergic reactions and vernal conjunctivitis exhibit eosinophils in large numbers in conjunctival scrapings. Occasionally there is an increase in basophils, the significance being the same. In contact dermatitis and conjunctivitis the eosinophil count is not increased.

Beal's conjunctivitis is characterized by the presence of large lymphocytes or monocytes. Leber cells may be observed in any case of chronic conjunctivitis.

The study of secretion smears and scrapings or of cellular reactions aids in the diagnosis of ophthalmic disease and is a guide to treatment. The ophthalmologist should make these examinations himself, rather than assign them to laboratories, for general bacteriologists do not know the significance of bacteria as found in the eye. Smears should be made in duplicate, one being stained by Gram's method and one with Wright's or Giemsa's stain. When possible, comparison with findings on culture should be made.

DISCUSSION

DR. FREDERICK A. LAUPPE: The terminology in bacteriology has changed greatly since many physicians were in medical school. The variation in virulence and cultural characteristics of organisms in different parts of the country accounts for the healthy differences of opinion regarding the pathogenicity of some of these organisms.

Bacterial growth in the conjunctival sac is discouraged by the lower temperature, the presence of lysozyme and the sluicing effect of the tears. The upper fornix is most likely to be sterile. A bilateral eye bandage will produce increased infection in conjunctivitis. The usual conjunctival flora includes a mixture of organisms, and, as Dr. Allen pointed out, the bacteria of the lid margin may differ from those of the conjunctival sac.

Clinical findings cannot be classified on a bacteriologic basis, for the same organism may produce different conditions; conversely, a certain clinical picture may be produced by different organisms.

Will Dr. Allen please state his opinion regarding the etiologic factor in marginal ulceration of the cornea?

DR. CECIL LEPARD: Has Dr. Allen had any experience with the use of aureomycin or streptomycin instead of silver nitrate in the prophylactic treatment of the newborn infant?

DR. LELAND CARTER: Please discuss the differential diagnosis of gonorrheal ophthalmia, inclusion blennorrhea and staphylococcic conjunctivitis.

DR. WALTER NEEB: What is the relative resistance of viruses to caustics in vitro?

DR. LELAND CARTER: Dr. Allen, why do you prefer penicillin by injection rather than by instillation?

DR. NEIL BENTLEY: Have you had any reactions to penicillin ointment?

DR. JAMES H. ALLEN, Iowa City: I wish to reemphasize that cultures should be taken from the lower fornix or the region of the caruncle. Organisms of the Staph. pyogenes group are normal inhabitants of the conjunctival sac. Some forms of Staph. pyogenes var. albus are nonhemolytic and nontoxin-forming. Disease is produced by the hemolytic staphylococci—Staph. pyogenes var. albus, var. aureus or var. citreus—these are also toxin producing. It is not practical to determine toxin production in clinical work.

Marginal ulcerations of the cornea may be produced by any organism which is capable of producing conjunctivitis—the staphylocci, the Morax-Axenfeld bacillus, the Streptococcus viridans group and others. In some cases no pathogen can be demonstrated, and it is possible that such infections may be due to as yet undiscovered viruses.

No active case of trachoma has been seen at the University of Iowa since my return from military service. The Trachoma Treatment School at Fort Apache has been discontinued.

For two years my associates and I have been investigating the prophylactic use of penicillin in the eyes of the newborn infant. In one series penicillin was given intramuscularly to the mother twenty-four hours before delivery and no treatment was given the baby. In another series one eye was treated with silver nitrate and the other with penicillin.

The Credé method has been unjustly criticised in many cases, although in some there is good reason for this criticism. The method used consists in instilling 1 drop of 1 per cent silver nitrate into each eye and holding the eyelids open for at least thirty seconds. This procedure is carried out immediately after delivery and is repeated three hours later, after the baby has had a complete bath, in order to prevent contamination from the skin. In a series of 13,000 deliveries over a period of eleven years there have been only 2 cases of gonorrheal ophthalmia, in 1 of which the baby's general condition was so bad that no treatment was given and in the other, a case of difficult labor, the use of silver nitrate may have been forgotten. Although there have been some cases of chemical conjunctivitis, there have been no serious sequelae.

Gonorrheal ophthalmia has a usual incubation period of three days and never appears after the fifth postnatal day unless contamination occurs after birth. If there is onset later than five days after birth the attendants should be suspected. When there is premature rupture of the membranes, it is possible to have the infection clinically present with corneal ulceration already developed at the time of birth. The early smears usually show no organism, but there is an abundant, foul, greenish yellow, purulent discharge.

Inclusion blennorrhea has an incubation period of seven to eight days and is characterized by a purulent discharge which is usually less severe, is not greenish and is less dirty appearing than that in gonorrheal ophthalmia. Edema is prominent, especially in the lower fornix. Conjunctival scrapings show the presence of inclusion bodies.

Conjunctivitis due to Staph. pyogenes may have an incubation period of one to four days, usually appearing after four days and being less severe and self limited. Smears usually show many staphylococci.

Viruses are resistant to caustics. The sulfonamides are virucidal or virustatic when administered locally or internally. They are used in treating trachoma and inclusion blennorrhea.

It is preferable to use penicillin locally in cases of mild infections, but for severe infections with ulceration parenteral or oral administration should be employed. The doses recommended are 100,000 units per gram of base in ointments, 100,000 units per 10 cc. in solutions and 100,000 to 300,000 units in each intramuscular injection. For pneumococcic ulcers of the cornea 300,000 units should be given every three hours for forty-eight hours. Reactions to penicillin occur in about 5 to 10 per cent of cases in which it is used locally. Streptomycin dermatitis is not uncommon and affects particularly the hands of nurses in tuberculosis sanatoriums. The additional use of antihistaminic substances may permit one to continue treatment with penicillin or streptomycin in sensitized persons.

Leland F. Carter, M.D., *President*

William S. Gonne M.D., *Secretary*

April 21, 1949

The Newer Antibiotics in Treatment of Acute Conjunctivitis. DR. ALSON E. BRALEY.

Tremendous strides have been made in antibiotic therapy during the past eight or nine years, but understanding of the use of antibiotics in combating virus infections has not advanced very well. Knowledge of the selective action of these drugs is essential to proper therapy.

Azosulfamide (neoprontosil) was discovered to be primarily effective against streptococci, and soon afterward sulfanilamide was found to be effective against streptococci and pneumococci, slightly effective against staphylococci and gonococci and of moderate value against organisms of the psittacosis group, including those of trachoma and inclusion blennorrhea. Sulfathiazole also exhibited selective action against gonococci, pneumococci and streptococci, but not against the viruses of trachoma, lymphogranuloma venereum or psittacosis, and was of questionable value against the virus of inclusion blennorrhea. Pneumococci, streptococci and gonococci were found to be very sensitive to sulfadiazine.

Tyrothricin and gramicidin are not very effective except against staphylococci.

Penicillin combats most types of staphylococci, streptococci, pneumococci and gonococci but has no effect on the virus of trachoma and other viruses.

Streptomycin is fairly effective against staphylococci, moderately so against streptococci and gonococci and very effective against many of the gram-negative bacilli. It is not of value against the viruses of trachoma or inclusion blennorrhea.

Bacitracin is slightly less effective against staphylococci than is penicillin but is extremely effective against some gram-negative and gram-positive bacilli.

Aureomycin exhibits activity much the same as streptomycin, except that it is not effective against some of the gram-negative bacilli but is of value in treatment of rickettsial disease, typhus, Rocky Mountain spotted fever and psittacosis. It has some effect against herpes simplex.

Sulfanilamide is the drug of choice against trachoma, but in general the antibiotics are not particularly effective against viruses. Aureomycin is a possible exception.

Any conjunctivitis which does not improve in from three days to two weeks is usually considered to be due to a virus infection or to allergy. Viruses, like bacteria, produce hyperacute, acute, subacute or chronic conjunctivitis. The conjunctival response is primarily follicular, whereas in bacterial disease it is primarily papillary, producing a velvety appearance.

Epidemic keratoconjunctivitis is a hyperacute form with early lacrimation and edema, and with the later development of membrane and corneal opacities, which may extend through the full thickness of the cornea. The virus can be isolated during the first five days—the period during which it is likely to be spread in the physician's office. Later, it is possible to neutralize the virus with the patient's own blood serum.

A series of 53 patients were treated with aureomycin, beneficial results being obtained in 20 per cent of the patients who started treatment in the first five days. The disease was arrested in three days, with no evidence of further development and without formation of corneal opacities. The use of aureomycin in treatment of this infection is definitely indicated until something better is available.

Penicillin or silver nitrate should not be used in cases of epidemic keratoconjunctivitis because the solution leads to extension of the infection. Penicillin is also a factor in the spread of the virus of herpes.

The virus of superficial punctate keratitis has not yet been reported in the literature. Short filaments may be formed in some cases of this disease. None of the antibiotics is known to be effective in this condition.

Dendritic keratitis and herpes simplex are similar. There are three types of herpes affecting the eye. The acute form is not unlike epidemic keratoconjunctivitis, producing hyperacute conjunctivitis with edema. It occurs only in children and runs its course in from two to three weeks. In two thirds of the patients the disease is effectively treated with aureomycin. The second type, which is recurrent throughout the patient's life, gives the best response to iodine. A high antibody

titer is developed. The history reveals the early development of herpes labialis. The third type is a severe acute form which follows herpes labialis and does not respond well to any treatment. Uveitis develops, and the eye may be lost. A trial of 0.5 per cent aureomycin borate every hour for forty-eight hours is warranted. If the infection is not improved at the end of that time, cauterization with iodine is in order. In about two thirds of the cases the condition improves.

The inclusion bodies of the various viruses differ in appearance when stained. The larger viruses show inclusion bodies within the cytoplasm of cells, whereas the smaller ones produce intranuclear inclusions. The herpes virus is of the latter type.

Molluscum contagiosum is a common infection, the diagnosis of which is usually missed and which may result in the development of acute conjunctivitis and superficial punctate keratitis with pannus formation. Special stains reveal the presence of a virus.

Verrucae are also due to virus infection and may produce conjunctivitis. Antibiotics are valueless in treatment. The inclusion bodies are intranuclear.

In cases of herpes zoster aureomycin has no therapeutic effect, either by intravenous or by oral administration.

Keratitis may be present in scrofuloderma, a condition from which the tubercle bacillus has been isolated. Aureomycin given intravenously and orally at the same time has proved effective in the treatment of this disease and is almost as good as streptomycin.

In a case of very severe marginal keratitis of unknown cause, but similar to rodent ulcer of the cornea, the response to aureomycin therapy was good.

DISCUSSION

Dr. Paul Cusick stated that most of his patients with dendritic keratitis have required iodine treatment, to which they all responded. He requested comments on vehicles for aureomycin methylcellulose in particular, and on treatment of infections with Pseudomonas aeruginosa and Proteus vulgaris. Dr. Gerald Spero asked about treatment of epidemic conjunctivitis and of the residual corneal opacities. Dr. Harold Falls, Ann. Arbor, Mich., requested more information on the intravenous and oral use of aureomycin and asked about complications. Dr. Edmond Cooper asked whether there had been any reports of sensitization due to local application of aureomycin. Dr. Herman Scarney showed slides of epidemic keratoconjunctivitis and reported that there have been excellent results from the use of aureomycin in this disease. He asked whether there was any value in controlling the p_H in treating this condition.

Dr. Alson E. Braley, New York: Aureomycin is less irritating if administered locally in substances of high viscidity, such as ethylenediamine or 0.25 per cent methylcellulose, but it loses its antibiotic activity sooner, at least in neutral solutions. Ointments have proved irritating in concentrations above 0.5 per cent. To retain effective antibiotic power, aureomycin must be in vehicles with a p_H of 3.5 or below and therefore is irritating when used locally. In less acid mediums it loses its activity rapidly. In local use aureomycin does not penetrate beneath the epithelium.

In ulcers due to Ps. aeruginosa streptomycin and aureomycin are not particularly effective. Experimentally, sulfadiazine powder is most

efficacious in treatment of these infections. Proteus vulgaris is variable in its reaction, some varieties being sensitive to streptomycin and some to aureomycin. No antibiotic is particularly effective in eradicating preoperative Proteus infections.

Foreign protein is valuable in treatment of acute epidemic keratoconjunctivitis, but only time is effective in removing the postepidemic opacities. Patients are more comfortable if treated with alkaline solutions or normal blood serum.

Adequate oral administration of aureomycin requires 1 to 2 Gm. per day and produces nausea because of the acidity of the drug (p_H 2.5 to 3.0). Patients frequently vomit part of the drug. Administration of neutral aureomycin compounds by mouth produces no effective level in the blood. In cases of virus pneumonia 1 Gm. per day is required for two or three days. In intravenous use a continuous drip of 250 cc. of dextrose solution or isotonic sodium chloride per hour is started, and 500 mg. of aureomycin is mixed with the saline solution and injected into the intravenous tubing. Up to 1 Gm. may be given in ten minutes. To date, the only reaction has been a mild chilly sensation. The concentration attained within the eye is four times as high by intravenous administration as by any other method.

In a case of severe pemphigus 1 Gm. of aureomycin was given daily for three weeks, with a fair result.

Because of sensitization, penicillin should not be used locally in the eye. Sulfacetimide, but not sulfadiazine, may be used locally, as may the other sulfonamides, because there is little cross sensitivity.

To date only 1 case of aureomycin sensitivity has been noted, but there will probably be many others as the use of the drug is increased.

Iontophoresis with aureomycin produced an acid burn of the cornea.

Generally it is not well to mix antibiotics. Penicillin and sulfonamides mixed are no better than penicillin alone.

Lindner stated that sulfacetimide is best in treatment of trachoma. I have seen few cases of this disease since introduction of that drug.

DETROIT OPHTHALMOLOGICAL SOCIETY AND DETROIT OPHTHALMOLOGICAL CLUB

Leland F. Carter, M.D., Presiding

Annual Joint Meeting, Dec. 16, 1948

Dr. Wesley Reid introduced the speaker of the evening, Dr. Parker Heath, a former member of both societies, and one of the founders and the first president of the Detroit Ophthalmological Society.

Correlation of Some Diseases of the Fundus and Their Pathology. Dr. Parker Heath, Boston.

[The speaker limited his discussion chiefly to retrolental fibroplasia and other conditions which might simulate this disease clinically or microscopically. The talk was illustrated by the projection of a large number of excellent pathologic slides.]

There are several theories of the etiology and development of retrolental fibroplasia, and present knowledge is in a confused state. Statistical studies in Boston showed an incidence of 30 per cent in the

approximately 200 premature babies weighing 4 pounds (1,814 Gm.) or less who are born in that city each year. The marked differences in incidence in various cities prompted comparative studies, and a recent statistical report by Kinsey and Zacharias from the Howe Laboratory of Ophthalmology, Harvard Medical School, suggests that certain factors in the care of the premature infant may contribute to the development of retrolental fibroplasia. The administration of water-soluble vitamin A, iron and oxygen, particularly a combination of the first two substances, appeared to be correlated with a high incidence of the disease. When vitamin A in oil was administered, the disease did not occur, an observation which suggests a possible factor in prevention and therapy.

Retrolental fibroplasia may be classified on a clinical or a pathologic basis. The pathologic diagnosis is relatively easy, but the clinical diagnosis is difficult because of many factors, including the various degrees of maturity of the affected eyes.

The first division includes eyes in which the lesions are primarily in the anterior segment and which may or may not be associated with prematurity. The most striking feature is the elongated ciliary processes. The anterior chamber is shallow. Variable degrees of plaque formation behind the lens or of opacities of the lens may be present, to produce a grayish mass. Although some eyes show retinal detachment, the retina and choroid are likely to be normal and fully differentiated. Persistent hyaloid vessels may be present. In this group there is 100 per cent failure of treatment except when the lesions are of minor degree.

The second division includes eyes in which the causative factor is hypoplasia of the secondary vitreous with the development of an unusually large amount of primary vitreous. The condition is usually, but not necessarily, found in premature infants. The eyes are smaller than normal, show fetal angles of the anterior chamber, undifferentiated retinal structures (second stage of differentiation) and microcornea. The lenses have remnants of fetal vessels anteriorly and posteriorly. The anterior chamber is not always shallow. The retina may be detached and cystic.

The third division includes eyes of similar appearance the pathologic changes in which are due to many causative factors, the primary lesion being in the retina. The retinal degeneration is much the same as that in angiomatosis and Coats's disease. Microscopically there are cystic changes, hyaline formation in the blood vessels and endothelial proliferation. The changes are reversible in some cases.

Among the several diseases with which retrolental fibroplasia may be confused are retinoblastoma, septic endo-ophthalmitis and toxoplasmosis. In the last condition the infant is likely to be premature and to have a partially differentiated retina, a fetal angle of the chamber and a round lens. Other conditions with which the disease is less likely to be confused because of the history, but which, nevertheless, have similar clinical and pathologic pictures, are tuberculoma of the choroid with retinal separation, metastatic carcinoma of the choroid and retinitis proliferans.

The studies on retrolental fibroplasia have brought the problem to the point where it is about to be solved.

DISCUSSION

DR. F. BRUCE FRALICK, Ann Arbor, Mich.: The variations in microscopic pictures illustrated by the slides explain the occasional removal of

an eye with retrolental fibroplasia, owing to a mistaken diagnosis. The differential diagnosis is not always easy, and if one or two consultants believe that there is the possibility of malignant growth in an eye removal is justified. Fortunately, most of the eyes are seen early in life, when some of Dr. Heath's "confusion pictures" are rarely confusing. In the usual eye with retrolental fibroplasia the pupil dilates poorly and the ciliary processes are pulled forward. Usually the lens is clear, with a membrane behind it which may have sufficiently thin areas to permit the examiner to obtain glimpses of the fundus.

The slides shown illustrate the futility of surgical corrective measures. In view of present knowledge, one should not make many mistakes regarding the necessity for enucleation, but one should not hesitate to request consultation.

Dr. Harold Falls, Ann Arbor, Mich.: A summary of the essential features of Dr. Heath's classification would be helpful.

Both Owens and Kinsey stressed the extremely high incidence of retrolental fibroplasia in premature infants. To date, there is no evidence of consanguinity or heredity in the Ann Arbor studies.

A case of retrolental fibroplasia which resembled angiomatosis retinae was observed in which there was a crow's foot type of termination of the vessels in the periphery with dilatation of the vessels. At frequent examinations the development of a fibroplastic sheet was observed, traction was apparent and the vessels shrank and became fibrous cords.

The new evidence regarding the possible influence of vitamin A in oil will be of value to pediatricians. The salient diagnostic point in retrolental fibroplasia is the prominence of the ciliary processes.

Dr. A. D. Ruedemann, Cleveland: It is difficult to see how any but the mildest forms can be reversible. The last types described are unlikely to cause confusion. Examination is usually troublesome, and this adds to the difficulty of diagnosis. Clarification of the classification is requested.

Dr. Parker Heath: Retrolental fibroplasia is not a new disease and has been found to occur in various animals, as well as man. The choice of the name is a poor one. Various causative factors may produce the same end picture. The end results seen at the retrolental fibroplasia clinic at the Massachusetts Eye and Ear Infirmary are depressing. There is no evidence of any relationship between brucellosis and retrolental fibroplasia.

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Feb. 17, 1949

Surgical Treatment of Glaucoma. Dr. John H. Dunnington, New York.

Dr. Dunnington discussed the reasons for failure of primary surgical treatment of glaucoma and offered suggestions for the prevention of such failures and for secondary operations if required. He first

pointed out that the two commonest causes of failure are (1) faulty selection of a surgical procedure and (2) faulty technic.

He cited the procedures of choice for various types of glaucoma as suggested at a symposium held at a recent meeting of the American Academy of Ophthalmology and Otolaryngology. He outlined the reasons for their selection and pointed out that paracentesis of the anterior chamber in cases of acute narrow angle glaucoma is inefficient, as is iridectomy in obstinate cases of this type.

He referred to Chandler's discussion of faulty technic and stressed correct technic as an important preventive factor. The cases of operative failure were divided into two groups: (1) those in which ocular tension remains high, and (2) those in which ocular tension subsequently rises.

In the first group fall most of the cases in which the original procedure was a poor choice, the best illustration being paracentesis for acute narrow angle glaucoma. Such a status calls for iridectomy or a filtering operation.

If the original operation was an iridectomy or a filtering procedure, hemorrhage or a damaged lens may be the cause of failure. A swollen cataractous lens must be removed promptly. Hemorrhage is a difficult problem and must be handled with great care. If absorption has not begun in forty-eight hours, a careful corneal paracentesis is recommended.

For hemorrhage into the vitreous, spontaneous absorption is preferred. Posterior sclerotomy in the region of the ora serrata may be considered, and if other procedures are unsuccessful nonperforating cyclodiathermy is worthy of trial.

Most cases of failure in glaucoma surgery fall in the second group. A careful survey to determine the cause of the secondary rise in tension was urged. If the cause is uveitis, either severe or quiet, the treatment should be the measures used in glaucoma secondary to uveitis, rather than a second operation. Spontaneous recovery in such cases is not infrequent, and the author advised waiting at least two months before performing a second operation in such a case. Miotics and mydriatics are used with great care. Ten per cent phenylephrine (neo-synephrine®) hydrochloride to keep the iris mobile is often useful when miotics are used.

Granted that a second operation is indicated, the multiplicity of procedures available is evidence of their frequent inefficiency. If an iridectomy has been done and the iris is healthy, an iridencleisis is preferred in cases in which tension is not over 45 mm. of mercury, and sclerectomy with inclusion of the iris, in the severer cases. If the iris is atrophic, a trephination is preferred. If there are peripheral anterior synechias, the site of the trephination should be chosen where these adhesions are minimal. One trephining does not preclude another at a different point, away from previously formed scars. Cyclodialysis is usually not helpful in the presence of a narrow or an obliterated angle. A combination of cyclodialysis and iridectomy was described for certain cases in which another filtering operation is not considered feasible.

Perce DeLong, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

April 21, 1949

Metastatic Carcinoma of the Eye. Dr. James N. Greear Jr., Washington, D. C.

This paper was published in the *American Journal of Ophthalmology* (**33**: 1015 [July] 1950).

DISCUSSION

Dr. Wilfred E. Fry: Dr. Greear has covered the subject of metastatic carcinoma of the eye very thoroughly. I can only emphasize some of the interesting points that he has discussed.

I think he is correct in his view of the frequency of metastatic carcinoma. In many cases the eye is not examined in detail because the patient is so ill that the general symptoms and prognosis overshadow any ocular complaint; moreover, in relatively few patients does the process go on to secondary glaucoma, when the services of an ophthalmologist become urgent. Another interesting feature that has been brought out is the relatively great frequency of metastatic carcinoma of the eye when the primary tumor is in the lung. This is much higher than most of us had thought. In most cases which I recall the mammary gland has been the seat of the primary tumor. Dr. Greear also pointed out that almost any structure in the interior of the eye may be involved in a metastatic lesion. Undoubtedly the structure most frequently involved is the choroid. Because other structures are involved, one does not necessarily conclude that the lesion cannot be metastatic. Still another feature that I thought important was the fact that occasionally the ocular tumor may appear to be primary, whereas in reality it is secondary to one elsewhere. I wonder whether Dr. Greear would discuss in more detail the cytologic features of some of these ocular tumors. He mentioned a case of tumor of the lung in which it was the initial opinion that the ocular involvement was primary, whereas the tumor in the lung was the primary lesion.

It may be worth while to mention briefly the three ways in which, as I recall it, most of these tumors manifested themselves clinically: (1) involvement in or near the macular region, (2) extensive retinal detachment and (3) secondary glaucoma. Illustrating the first manifestation is a patient, a woman aged 35, who had been under my care for some time and whose refraction I had determined several times. Her initial symptom was disturbance of vision, and the only ophthalmoscopic sign was haziness in the macular region. In the course of time this developed into the more or less typical appearance of a metastatic intraocular growth. The history aided in the diagnosis. There had been radical mastectomy for carcinoma, but at the time at which the ocular symptoms developed a survey showed no metastases in the chest or other structures. She died about eight months after the first appearance of her ocular symptoms.

The second type of involvement is illustrated by the case of a woman of about 40 who had also had a radical mastectomy three years previously. The occasion for my seeing her was rather rapid loss of

vision in one eye. At that time there was extensive detachment of the retina. The detachment occurred fairly rapidly, following any loss of vision.

The third type, secondary glaucoma, was illustrated by another case, then under observation, in which the secondary glaucoma followed rather rapidly the initial appearance of choroidal lesions. The diagnosis was not difficult, since roentgenographic examination of the spine revealed metastatic lesions. The eye had to be removed because of secondary glaucoma, and the patient died within a year.

We are indebted to Dr. Greear for this excellent coverage of the subject.

DR. JOHN S. MCGAVIC, Bryn Mawr, Pa.: Dr. Greear has, in his usual fashion, presented an enjoyable, as well as scientific, paper.

There are two reasons for the fact that available statistics do not reflect a higher incidence of metastatic lesions in the eye. 1. Few ophthalmologists see more than a case or so and are not likely to report it singly. 2. Tumor specialists are not easily interested in unusual sites of metastasis, nor do they look on the ophthalmologist as cutting much of a figure in cancer work. They, therefore, do not invite him in when metastasis might best be seen. On the other hand, it has been pointed out that metastatic lesions sometimes appear before the primary tumor is suspected. The eye in such a case has recently been sent us at the laboratory by Dr. P. Robb McDonald, who removed the eye post mortem. The patient, a man aged 65 with carcinoma, had detachment of the upper portion of the retina. The process involved the upper portion of the optic nerve, and I am told that the nerve appeared as though it were split. Operation was not performed, but careful search for a primary lesion was made, since a metastatic lesion was suspected, but no primary tumor was found. The patient died shortly, and the diagnosis was bronchogenic carcinoma. The specimen of the eye was interesting because about 90 per cent of the neoplastic tissue in the choroid was necrotic. It has been my privilege to examine about 8 patients with metastatic carcinoma, most of them at Memorial Hospital, New York. One had a metastasis to the optic nerve, which responded promptly to radiation therapy, with clearing of the field defects. Two had metastases to the choroid with separation of the retina. These also responded to radiation therapy during the short period of survival. Apparently, the necrosis of the tumor caused by the radiation is responsible for the production of chorioretinal adhesions, which can be seen developing during the period of treatment. Because the life expectancy of the patient is short and the latent period for development of radiation cataract is long, the situation is an ideal one in which to use radiation, and it can be extremely helpful in preserving or restoring vision in persons whose lives will be none too happy. The preservation of vision is especially appreciated by patients who are otherwise incapacitated.

The manner of growth of metastases has been well covered. It is rather striking how many patients whose tumors are not primary in the lungs do have pulmonary involvement, as observed either clinically or post mortem, when they have ocular metastases. Both clinically and on section the separation of the retina in these cases appears far more extensive than it is with primary tumors of the same size, such as malignant melanoma, with which the retina is commonly adherent to

the tumor. There are several situations in which one would suspect a metastatic lesion without other evidence. 1. If the detachment is bilateral, the lesion would not be a melanoma. 2. If the detachment is very diffuse and there is any area of reduction in the transillumination, this area would be much smaller than the area of detachment. It is generally known that transillumination is much less interfered with in metastatic tumors than in solider tumors, such as melanomas. 3. If the subretinal fluid when the patient is examined upright has shifted from its position when the patient was lying flat, the probability of a metastatic lesion is greater. This point is of the greatest practical significance; I know of 2 cases in which the difference was impressive.

Several years ago I had about 45 sections collected from here and there showing metastatic tumors of the eye. In 41 of these the choroid was involved. In 1 the optic nerve and choroid were involved; in 2, the choroid, iris and ciliary body, and in 2 the iris and ciliary body alone. In 8 sections the tumor involved the iris, and in 2 only was the iris involved alone; in the remainder the growth involved either the ciliary body or the choroid or both, together with the iris. Why there is less involvement of the ciliary body than of the choroid or of the iris alone has not been explained. In tumors that involve the iris only one feature is distinct, and that was illustrated by Dr. Grecar—the portion of the tumor extending to the posterior surface of the cornea is much more extensive than is usual in malignant melanoma or leiomyoma.

It is not unusual for persons to have more than one malignant tumor. It is not always possible while the patient is alive to decide which tumor gave rise to the metastatic lesion. For example, one patient had a radical mastectomy for carcinoma, and about three or four years later a tumor developed in the iris. The eye was removed, and supposedly there was a metastatic carcinoma, but it proved to be a lymphoma. The patient was alive and well five years later, showing no evidence of either carcinoma or lymphoma.

Two years is generally given as the longest period of survival, but von Sallmann has reported a case in which the patient was alive three and a half years after enucleation of the eye. Such unusual instances lead one to the conclusion that these metastatic tumors should be treated actively. I should not take quite such a dim view of the prognosis, although the patient is almost sure to die of the cancer. Since 20 to 33 per cent of metastatic tumors of the eye are bilateral, it would be, I think, a mistake to enucleate even one eye except for blindness or relief of pain. Furthermore, I believe that the primary lesions should be treated actively, even if it requires major surgical treatment, since one is not always sure that a metastatic lesion is carcinomatous and that it comes from the suspected source.

Yesterday, Dr. McDonald sent an interesting specimen to the laboratory. The patient, a 36 year old woman, had had a mastectomy two years previously. There was no clinical evidence of metastasis elsewhere, but she had a detachment of the retina which appeared serous. Dr. McDonald suspected metastatic carcinoma. There was no hole in the retina. Although the detachment appeared serous, no fluid was released at operation. A second operation was performed, at the request of the patient, as the first was not successful. At the second operation

no fluid was obtained; so Dr. McDonald sent a trephine button of sclera and some attached tissue to the laboratory, with the request that we look for carcinomatous cells. Such cells were present. This case is rather unusual.

Dr. Perce DeLong: In 1932 I reported a case of carcinoma of the choroid before this Section. At that time I felt that the tumor was a rare pathologic entity, but several of my confrères in Philadelphia told me that if I would come to certain hospitals they would show me several cases. I visited three institutions; there I found patients with advanced carcinoma, usually bedridden, and, to my amazement, I found 7 instances of solid detachment of the choroid, which were in all probability metastatic manifestations.

The ophthalmologist does not as a rule see such patients, because they are not ambulatory. I was informed that in many instances the last stage of carcinoma is associated with definite ocular symptoms, with reduction of vision and pain.

Dr. James N. Greear, Washington, D. C.: One of the interesting features of metastatic carcinoma of the eye was the degree of pain which these patients apparently experienced, even in the absence of glaucoma. Pain may be present when there is no rise in tension and the eye is relatively free from inflammatory disturbance. In 5 of the 44 cases studied at the Army Institute of Pathology the patient complained of dimness of vision as the first symptom of the carcinoma. In some of these cases the eye was removed because it was thought to contain a malignant melanoma.

I have not seen any cases of metastatic carcinoma of the eye arising from a primary carcinoma of the uterus.

Radiation therapy is of great importance when both eyes are involved, particularly when there was a life expectancy of several months.

Since detachment of the retina may occur early in metastatic carcinoma of the choroid, bilateral detachment of the retina should lead one to suspect metastatic carcinoma.

Considered judgment should be employed in advising surgical measures, particularly major procedures, when one is relatively assured of general metastasis.

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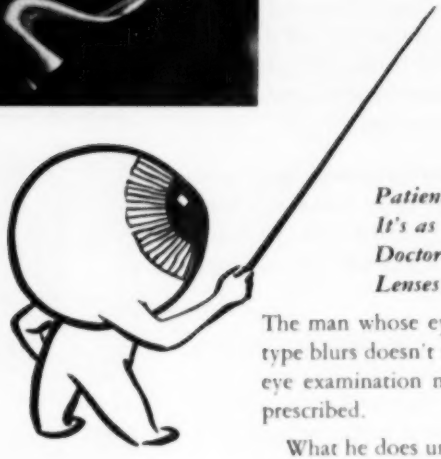

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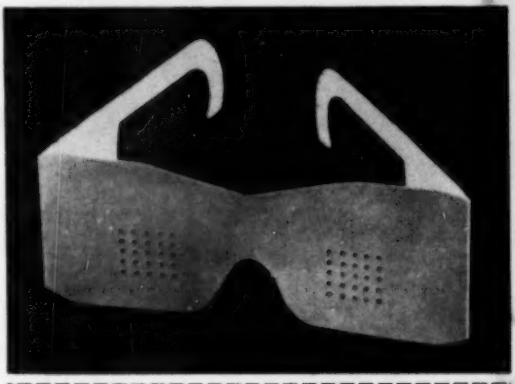

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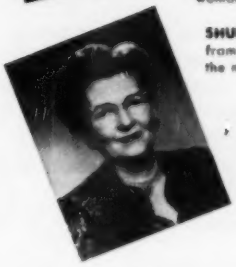

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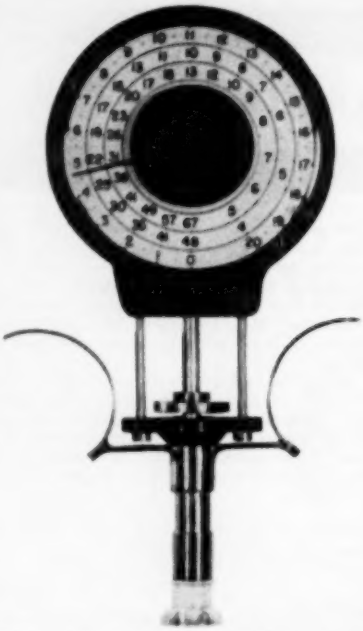

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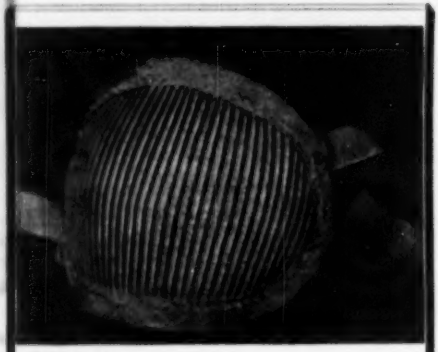

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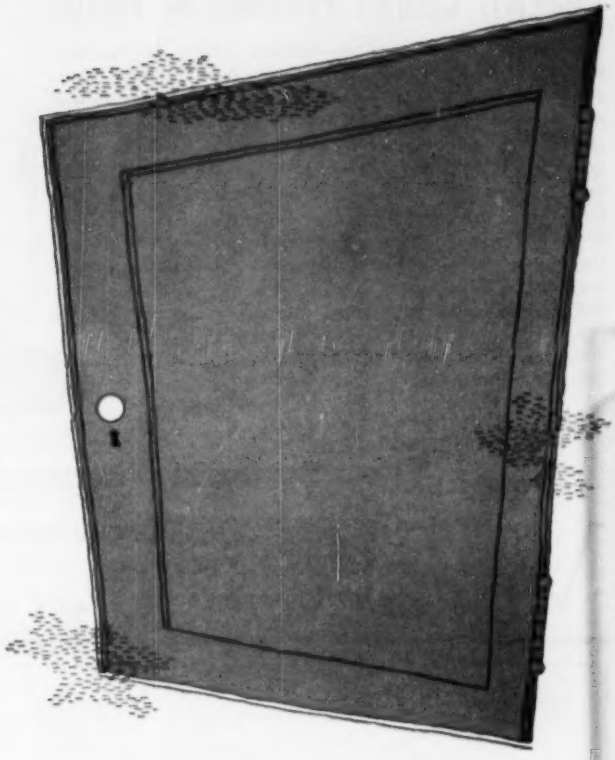

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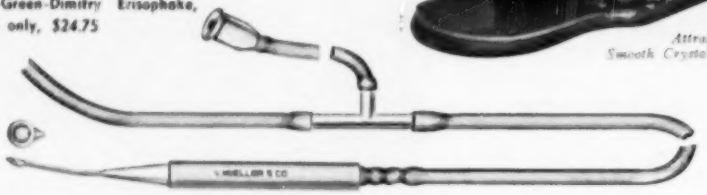

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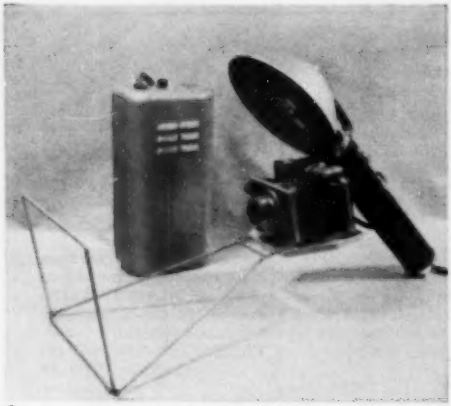

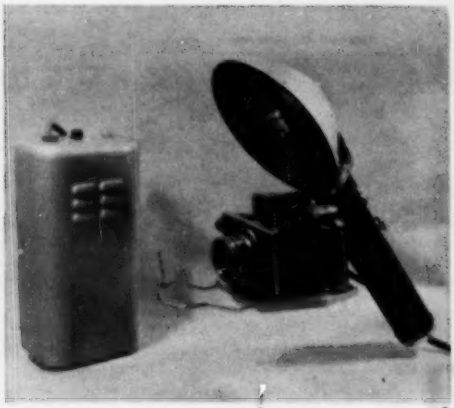

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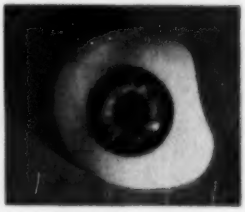

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